0 (21.2% total no. pts), 1 (57.6%), 2 (21.2%); n° metastatic sites: 1 (9.1%), 2 (48.5%), 3+ (42.4%).

Dose level	Raltitrexed (mg/m²)	UFT (mg/m²)	No. pts	DLT (G3/4)	Toxicity	Objective Response
1	2.0	200	3	0		1 PR, 1 SD, 1PD
2	2.5	250	6	1	1 pts Diarrhoea (G-3)	1 PR, 4 SD, 1 PD
3	2.5	300	3	0		1 PR, 2 SD
4	3.0	250	3	0		1 PR, 2 SD
5	3.0	300	6	1	1 pts Diarrhoea (G-3)	3 PR, 3 SD
6	3.0	350	6	2	1 pts Mucositis (G-3) 1 pts Neutropenia (G-3)	1 PR, 3 SD, 2 NA
7	3.5	300	6	3		

PR: Partiel Response; SD: Stable Disease; PD: Progresion Disease; NA: Not Avalaible. DLT was Diarrhoea, vomiting and neutropenia at level 7.

Conclusions: These results confirm that recommended dose for the combination of Raltitrexed and UFT is the same as recommended doses for monotherapy, Raltitrexed 3 mg/m², every 3 weeks on days 1 and 21, and UFT 350 mg/m², on days 1 to 28, followed by 2 weeks' rest of a 6 weeks cycle.

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First line simplified FOLFOXIRI in metastatic colorectal cancer (MCRC) patients (pts): results of a phase II study.

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Background: In our previous phase I-II study (Falcone et al, J Clin Oncol 2002) first line FOLFOXIRI (CPT-11 125-175 mg/sqm 1h IV infusion on day (d) 1, oxaliplatin (LOHP) 100 mg/sqm 2h IV infusion on d1, l-LV 200 mg/sqm 2h IV infusion on d1, 5-FU 3800 mg/sqm 48-h IV chronomodulated continuous infusion starting on d1, repeated every 2 weeks) demonstrated high antitumor activity (ORR=71.4%) and promising efficacy (median PFS=10.4 months and median OS=26.5 months) in MCRC. However this regimen required a chronomodulated infusion of 5-FU and because of neutropenia 60% of pts received G-CSF and delivered dose intensity was approximately only 78% of planned. Therefore we conducted the present phase II study to evaluate the safety and the activity of a simplified FOLFOXIRI regimen which could be more easily feasible in a multicenter setting.

Patients and methods: A total of 32 pts with unresectable MCRC received CPT-11 165 mg/sqm d 1, LOHP 85 mg/sqm d1, l-LV 200 mg/sqm d1, 5-FU 3200 mg/sqm 48-h continuous infusion starting on d1, repeated every 2 weeks: median age was 63 yrs (43-74), ECOG performance status was e 1 in 14 (44%) pts, 17 (53%) pts had multiple metastatic sites and 9 (28%) were pretreated with 5-FU or raltitrexed.

Results: All 32 pts were evaluated for safety and more relevant toxicities were: grade 4 neutropenia (34%), febrile neutropenia (3%), grade 3 thrombocytopenia (3%), grade 3 diarrhea (16%), grade 3 stomatitis (6%) and grade 3 peripheral neurotoxicity (3%); no toxic deaths occurred. Intention to treat analysis for activity showed 4 CR, 19 PR, 5 MR, 2 SD and 2 PD for an overall response rate (CR+PR) of 72% (95%CI: 53-86%). Median duration of responses was 10.5+ months; 7 (22%) pts with residual liver or lung metastases were radically resected after chemotherapy. After a median follow up of 13.4 months median PFS was 10.8 months and median survival has not yet been reached.

Conclusions: This simplified FOLFOXIRI combination has manageable toxicities and significant antitumor activity in MCRC pts. Therefore the Gruppo Oncologico Nord Ovest (GONO) has started a randomized multicenter phase III study comparing this regimen to standard FOLFIRI.

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A study of capecitabine in elderly patients as first line treatment in advanced or metastatic colorectal cancer

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Background: Determine the efficacy and toxicity profile of a twice daily oral capecitabine administration at 2500 mg/m²/day as first line in elderly patients with advanced or metastatic colorectal cancer.

Material and methods: Patients aged ≥70 years with advanced or metastatic colorectal cancer (CRC) histologically confirmed, who had not received prior chemotherapy, at least 1 measurable lesion (RECIST), ECOG ≤ 2 and bone marrow, renal and hepatic function adequate, were eligible for this open label study. Patients were treated with oral capecitabine at 2500 mg/m²/day 2 weeks in a 3 weeks course. This scheme was repeated in 8 cycles. This dose of capecitabine should be reduced, as established in the protocol, to capecitabine 1875 mg/m²/day when toxicity grade II-III occurred. Toxicity was evaluated every cycle using WHO toxicity criteria.

Results: 51 patients (pts) have been included in this analysis (M/F 31/20), median age 75 years old (71-90). ECOG 0:14(27.5%), 1:30(58.8%), 2:7(13.7%). 81.6% had not comorbidity, 78.3% had mild independence from any help (Barthel Index) and most of them (M/F 60.7%/44.4%) were autonomous (Lawton Index). Median of metastatic locations was 1 (62.5% with 1 location and 37.5% with 2 location or more) located mainly in liver (66.7%) and lung (33.3%). Up to date 50 pts received a total of 223 cycles (median 4, range 1-8), median relative dose intensity of 0.88. All these pts were evaluated for safety analysis. Grade III/IV toxicities per pt included thrombocytopenia(4%), leucopenia(2%), neutropenia(2%), diarrhea(6%), asthenia(6%), dyspnea(6%), nausea(2%), vomiting(2%), epigastric pain(2%), liver(2%), renal(2%), hand-foot syndrome(2%), anorexia(2%), abdominal pain(1%), thoracic pain(1%), and hyperglycemia(1%). There was not any significant differences in grade III/IV toxicities between the general population and the population over 80 years of age. Efficacy: To date 10 pts were not evaluable for response: 5 early withdraw (2 due to toxicity and 3 exitus), 3 dropped-out without efficacy evaluation and 2 are still undergoing treatment. 40 pts were evaluable for efficacy, 1 achieved CR, 9 PR, 22 SD and 8 PD resulting in an ORR of 25% (CI 95%: 11.6-38.4%). Median time to progression was 7.9 months. Nine pts (28.1%) obtained clinical benefit during treatment.

Conclusion: Twice daily oral capecitabine in elderly patients seems to be a well tolerated first line treatment in patients with advanced or metastatic CRC.

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Optimal dosing schedule for combination therapy with capecitabine and irinotecan in a human colorectal cancer (CRC) xenograft model

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Background: Capecitabine (Xeloda®) and irinotecan (CPT-11) are highly active single agents for the treatment of advanced/metastatic CRC. Recently, several clinical studies of capecitabine/irinotecan combinations have been performed in the EU and US, and high antitumor activity has been demonstrated. However, neutropenia and diarrhea have been reported to be dose-limiting toxicities of the combination, and a modality to reduce these adverse effects would be helpful. The present study was conducted to establish an optimal schedule of the combination in murine models that maintains potent antitumor activity but shows no increase in diarrhea.

Methods: Gastrointestinal toxicity in mice was estimated by observing the feces and by detecting occult blood in the feces using an occult blood testing kit (Shionogi). Antitumor efficacy was evaluated in a human colon cancer COLO205 xenograft model.

Results: We first used a murine model to examine the dosing regimen of single-agent irinotean, which is capable of inducing delayed-type gastroin-

testinal toxicity. Single injection of irinotecan at 120 mg/kg (MTD) did not induce diarrhea. In contrast, i.v. injection of irinotecan at 100 mg/kg/day, administered three times every other day, caused gastrointestinal toxicity. We then compared three different schedules of the capecitabine/irinotecan combination. Irinotecan was given i.v. at 100 mg/kg/day on days 1, 3 and 5 with capecitabine being given p.o. 539 mg/kg/day daily for 14 days either simultaneously or sequentially. Both capecitabine and irinotecan caused diarrhea when administered as single agents. With the simultaneous schedule, the diarrhea was more severe compared with the irinotecan-alone or capecitabine-alone groups. In contrast, with the sequential schedule, in which capecitabine was given after 3-day or 1-day treatment intervals following irinotecan injections, diarrhea was no more severe compared with the single-agent groups. In COLO205 xenograft model, the antitumor activity of irinotecan in combination with capecitabine showed additive activity at all of the examined schedules. The efficacy of the sequential schedule was the same as the simultaneous schedule.

Conclusions: A sequential administration schedule of capecitabine and irinotecan appears to be equally effective and better tolerated than the simultaneous administration schedule. Clinical studies of sequential capecitabine and irinotecan in patients with CRC could be warranted.

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Capecitabine combined with radiotherapy in Chinese patients with advanced or relapsed rectal carcinoma

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Background: Capecitabine (Xeloda®) is a tumor-activated oral fluoropyrimidine, which is preferentially converted to 5-FU by exploiting the higher concentrations of thymidine phosphorylase in tumor tissue compared to normal tissue. In addition, radiotherapy upregulates thymidine phosphorylase in tumor cells but not in normal tissues. Combining capecitabine with radiotherapy further upregulates TP. This trial was designed to evaluate the synergistic effect and safety of capecitabine combined with radiotherapy in Chinese advanced or relapsed rectal carcinoma patients.

Methods: 59 patients (pts) were enrolled from June 2002 to March 2003. All had measurable advanced or relapsed rectal carcinoma, Karnofsky performance status ≥60, adequate bone marrow, renal and hepatic functions. Prior radiotherapy to other sites or adjuvant fluoropyrimidines (≥1 month previously) were permitted. We used a total irradiation dose of 60 Gy (1.8 Gy/d) over approximately 6 weeks and capecitabine 825 mg/m^2 twice-daily including weekends for the duration of radiotherapy.

Results: 38 pts are currently evaluable for safety and efficacy: 22 men and 16 women; median age 50 years (range 36-74); measurable lesions: rectum (18), pelvis (18), skin (5), others (4). Thirty-six pts were recurrent, 2 pts were previously untreated. Previous treatment: 3 pts radiotherapy, 13 pts adjuvant fluoropyrimidines. There were few grade 3 adverse events: Hand-Foot Syndrome (HFS) 2 pts (5%), diarrhea 1 pt (3%). There was no grade 4 toxicity. Most common adverse events (>20% grade 1-2) were leukopenia 15 pts (40%), HFS 13 pts (34%), diarrhea 9 pts (24%) and thrombocytopenia 8 pts (21%). At the end of treatment, there are currently 2 complete responses (6%), 15 partial responses (58%) and 11 patients with stable disease (29%). Median progression-free and overall survivals have not yet been reached.

Conclusion: Oral, tumor-activated capecitabine combined with radiotherapy has proven to be a highly active regimen in Chinese advanced or relapsed rectal carcinoma patients and is well tolerated.

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E-cadherin expression is commonly downregulated by promoter methylation in colorectal cancer cell lines.

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Background: E-cadherin, a cell adhesion molecule, is regarded as a tumor/invasion suppressor molecule. In our preliminary study for 94 colorectal cancer patients, reduced or lost expression of E-cadherin were observed in cancer tissues in comparison with matched normal mucosa. By using six colorectal cell lines, we aim to explore whether the methylation of the E-cadherin gene is responsible for the silence of E-cadherin protein expression.

Methods: Methylation status of the E-cadherin gene was investigated by a highly quantitative real time PCR (Taqman) method. The extent of methylation was expressed as methylation index. Protein levels of the E-cadherin were measured by western blotting. For E-cadherin low/negative cell lines, 5-Aza-2'-deoxycytidine, a demethylation agent, was applied with concentrations from 2um to 4 um for 4-6 days.

Results: Four out of six colorectal cell lines (Dukes B, C, C and D respectively) had low or absent E-cadherin. The other two cell lines (one Dukes C and another Grade I) expressed high levels of E-cadherin. Apparent methylation in the promoter region of the E-cadherin gene was observed in three E-cadherin low/negative cell lines. Treatment of 5-Aza-2'-deoxycytidine induced the re-expression of E-cadherin protein in these three cell lines.

Conclusion: Our results suggest that aberrant promoter methylation of the E-cadherin gene may play a role in the down-regulation of E-cadherin in colorectal cancers.

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Serum concentrations of MMP-2 and TIMP-1 are of independent prognostic value for cancer specific survival in patients with metastatic colorectal carcinomas under chemotherapy

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Background/Aim: Matrix-metalloproteinases (MMP) and their inhibitors (TIMP) are playing a major role in the invasion, angiogenesis and metastasis of colorectal carcinomas. Recently we could show the predictive meaning of MMP-2 and TIMP-1 during chemotherapy. In this study we analysed the prognostic value of different serum markers for survival of patients with metastatic colorectal cancer.

Material and methods: 49 patients presenting with metastatic colorectal cancer received first-line chemotherapy consisting of 5-FU / FA as a 24-h infusion (AIO regimen) in combination with (n=24) or without (n=25) oxaliplatin, respectively. Prior to treatment, serum was obtained of all 49 patients and analysed for circulating concentrations of collagen IV, VI, tenascin, MMP-2 and TIMP-1 (Bayer Immuno Analyser). Probes of 100 healthy persons were taken as control.

Results: The median cancer specicfic survival (CSS) of the 49 patients was 22 months. Serum concentrations of >541 ng/ml for MMP-2 and <1002 ng/ml for TIMP-1 were significantly associated with an improved survival, respectively. Cox regression analysis revealed these two markers as of independent significant value (p=0.043 for TIMP-1 and p=0.009 for MMP-2, respectively). All the other clinicopathological criteria (e.g. age, gender, chemo-regimen) as well as the concentrations of the other serum markers did not contribute to survival.

Conclusions: Serum concentrations of MMP-2 and TIMP-1 prior to treatment were shown to be independent prognostic factors for CSS survival in patients with metastatic colorectal carcinomas undergoing a palliative first-line chemtoherapy. Bearing in mind their predicitive value these both serum markers are promising new tumour markers in colorectal carcinoma treatment.

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A phase II trial of aroplatin (L-NDDP), a liposomal DACH platinum, in patients with metastatic colorectal cancer (CRC) – a preliminary report

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Aroplatin (L-NDDP) is a liposomal formulation of *cis-bis*-neodecanoato-*trans*-R, R1,2-diaminocycloxhexane (DACH) platinum. L-NDDP is a structural analog of oxaliplatin, which was recently approved for the second-line therapy in patients with metastatic CRC.

We have initiated a phase II trial of L-NDDP in patients with metastatic CRC refractory to 5-fluorouracil/leucovorin or capecitabine and irinotecan therapy. Patients with history of prior oxaliplatin therapy were excluded. The starting dose level for L-NDDP was 300 mg/m^2 with possible intra-patient dose escalation up to 375 and 470 mg/m^2. The L-NDDP is administered