local recurrence, age, intraarterial administration, agents used in combination, previous radical surgery and platelet count, but significantly ($p < 0.05$) better in patients with only one site involved, hemoglobin (HGB) levels $\geq$ 125 g/l, peripheral blood leukocyte count (PBLC) $< 8 \times 10^9$/l, absence of liver metastases, and CEA < 100 µ g/l. Longer survival of borderline significance was observed in patients with duration of advanced/metastatic disease $\geq$ 21 months ($p = 0.13$) and interval from last CPT administration < 3 months ($p = 0.07$). These parameters were further examined by multivariate analysis, and HGB < 125 g/l (HR = 2.86), PBLC $< 8 \times 10^9$/l (HR = 0.45), duration of advanced/metastatic disease < 21 months (HR = 2.13), interval from last CPT administration < 3 months (HR = 0.42) and CEA < 100 µ g/l (HR = 0.49) were significantly ($p < 0.05$) associated with survival. HGB, PBLC, CEA and duration of advanced/metastatic disease, but not interval from last CPT administration retained statistical significance when the survival was measured from last CPT administration. Although the survival was similar among the 25 patients treated by TOMOX, there were 4 early deaths after this regimen.

Conclusions: More than 40% of patients pretreated by CPT survived 1 year after start of OHP therapy, and median survival from the diagnosis of advanced/metastatic disease in this selected group of patients was almost 3 years. The therapy was similarly effective as second or higher line of treatment. HGB, PBLC, CEA, and duration of advanced/metastatic disease were independent factors associated with survival. The number of early deaths observed after TOMOX is alarming.

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Patterns of failure after liver resection in patients receiving FOLFOX4 for metastatic colorectal cancer (MCRC) limited to the liver: a North Central Cancer Treatment Group (NCCTG) phase II study

S. Alberts[1], J. Donohue[1], M. Mahoney[1], W. Horvath[2], W. Sternfeld[2], S. Dakhil[3], R. Levitt[4], K. Rowland[5], D. Sargent[1], R. Goldberg[1]. *[1] Mayo Clinic, Medical Oncology, Rochester, MN, USA; [3] Wichita CCOP, Medical Oncology, Wichita, KS, USA; [4] MeritCare Hospital CCOP, Medical Oncology, Fargo, ND, USA; [5] Carle Cancer Center, Medical Oncology, Urbana, IL, USA*

Background: Bismuth et al pioneered treatment of patients with non-optimally resectable liver limited MCRC with oxaliplatin/5-fluorouracil (OXAL/5-FU) regimens to allow resection. (Sem Oncol 1998). We have reported results on the response in 42 eligible patients (Proc Annu Meet ASCO 2003), enrolled in an NCCTG trial designed to confirm Bismuth's findings. We now report on patterns of failure.

Methods: Patients with liver only MCRC deemed not optimally resectable by a liver surgeon received biweekly OXAL 85 mg/m^2 on d1 followed by leucovorin (LV) 200 mg/m^2, 5-FU 400 mg/m^2 bolus IV, then 22-hour infusion 5-FU 600 mg/m^2 on d1; repeated d2 (FOLFOX 4). Responding patients were reassessed for resectability. Surgical response was classified as 1) completely resectable (S-CR), 2) partially resectable (S-PR), or 3) unresectable (S-UR). Study design specified accrual of 39 patients, with 2 or more S-CRs indicating promising activity. 43 patients were accrued with follow-up available on all patients.

Results: 26 patients (62%) had tumor reduction (1-CR, 21-PR, 4-REGR) by pre-operative imaging. 17 patients (41%, 65% of responders) have undergone surgery (14 S-CR, 1 S-PR, and 2 S-UR) after a median of 6 months of chemotherapy (range 3 - 17). With a median post-surgical follow-up of 14 months (range 6 ñ 27), 10 recurrences have occurred in S-CR and S-PR patients (67% of resected patients). 36 patients have had progression or recurrence which occurred most frequently in the liver (9/12 surgical patients, 19/23 non-surgical patients). Other sites included: lung, colon, abdomen, bone, neck, peritoneum, and a new primary. Of all patients, 25 have died. Median survival is 27.9 months (95% CI: 20 ñ 34).

Best Outcome	No Progression or Recurrence	Progression or Recurrence Site		
		Liver Only	Non-liver Only	Both
Surgical (N = 17)				
S-CR & S-PR	5	6	3	1
S-UR	0	0	2	1
PR/REGR	1	8	0	0
Stable	1	6	4	0
Progression	0	5	0	0
Too early	1	0	0	0

Conclusions: Our data suggest that OXAL/5FU/LV has a very high response rate in liver limited MCRC and allows for successful resection of initially not optimally resectable patients in many cases. However, a high recurrence rate (71%) after surgery was observed, of which 67% (8/12) involved hepatic disease. Our trial supports the findings of Bismuth (1998) and further trials are indicated to enhance the promising observed results. Novel therapies are now being explored to further reduce the rate of recurrence. Supported by NIH Grant CA25224-18 and Sanofi-Synthelabo.

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A phase II study of preoperative oxaliplatin, capecitabine, and external beam radiotherapy in patients with locally advanced rectal adenocarcinoma: the RadiOxCape study

B. Honhon[2], L. Duck[1], B. Coster[3], J.-C. Coche[4], J.-L. Canon[5], P. Scalliet[1], C. Sempoux[1], Y. Humblet[1], A. Kartheuser[1], J.-P. Machiels[1]. *[1] Université Catholique de Louvain, Clinique des pathologies tumorales du Côlon et du Rectum, Brussels, Belgium; [2] Hôpital St-Joseph, Service d'Oncologie médicale, Charleroi, Belgium; [3] Hôpital St-Joseph, Service de Radiothérapie, Charleroi, Belgium; [4] Clinique St-Pierre, Service de Gastroentérologie, Ottignies, Belgium; [5] Hôpital Notre-Dame, Service d'Oncologie médicale, Charleroi, Belgium*

Local recurrence after surgery is a life-threatening problem in locally advanced rectal cancer. Preoperative radiotherapy is the standard of care for locally advanced tumors in many European countries and can decrease the local recurrence rate. Capecitabine and oxaliplatin are both active anticancer agents in the treatment of patients with advanced colorectal cancer and have radiosensitizing properties. Therefore, oxaliplatin and capecitabine may improve the effectiveness of preoperative radiotherapy in term of local control as well as prevention of distant metastases. This study was designed to investigate the efficacy (based on pathological response rate) and safety of preoperative chemoradiation in patients with locally advanced (clinical T3-T4 and/or N+) rectal cancer. Radiotherapy was administered for 5 weeks, 5 days a week (1.8 Gy/fraction, total dose 45 Gy, 3D conformation technique) in combination with oxaliplatin (50mg/m2 intravenously, weekly for 5 weeks) and capecitabine (825 mg/m2 orally, twice a day, each day of radiation). Since December 2002, 20 pts were accrued. Here, we report the preliminary data of acute toxicity during the administration of radiochemotherapy on the first 12 pts (ECOG 0-2; median age 55 y, ranging from 32 to 76; males/females 4/8). Radiotherapy was administered as planned to all patients. Grade III NCI-CTC toxicities were diarrhea (3 pts), vomiting (1 pt), and fever (1 pt). No grade IV toxicity was observed. One patient experienced grade 1 neurotoxicity. Dose adjustment had to be performed in only 3 pts. Oxaliplatin alone was reduced in 2 patients: total oxaliplatin dose received was 80% and 70% of the planned dose, respectively. Oxaliplatin and capecitabine were both reduced in the third patient: total doses administered of capecitabine and oxaliplatin were 86% and 90% of the planned dose, respectively. The main reasons to reduce chemotherapy dosages were grade III diarrhea and fever. These results demonstrate that preoperative oxaliplatin and capecitabine in combination with radiotherapy is feasible in patients with locally advanced rectal cancer. Updated data about safety will be presented at the meeting on 20 pts at least.

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Phase I dose-escalation study with Raltitrexed ('Tomudex') combined with UFT in metastatic colorectal cancer.

J.R. Mel[1], J.M. Vieitez[2], P. Garcia-Alfonso[3], M. Gonzalez-Baron[4], E. Alvarez[1], A. Jimenez-Lacave[2], J. Nuevo[5], R. Cajal[5], H. Bovio[5]. *[1] Hospital Xeral Calde, Oncology, Lugo, Spain; [2] Hospital Central de Asturias, Oncology, Oviedo, Spain; [3] Hospital Gregorio Marañón, Oncology, Madrid, Spain; [4] Hospital La Paz, Oncology, Madrid, Spain; [5] Astrazeneca Spain, Medical Departement, Madrid, Spain*

Aims: Preclinical studies show synergism with Raltitrexed (Tomudex') given prior to 5-FU and preliminary clinical data indicate promising response rates. This study was initiated to determine the maximum tolerated dose, recommended dose and safety of this combination.

Patients and methods: Chemo-naive patients (pts) with metastatic, aged $\geq$ 18 years $\leq$ 75, WHO performance status score $\leq$ 2, satisfactory haematological, renal and hepatic function, life expectancy of at least 3 months, and at least one assessable or measurable lesion. Treatment schedule: patients received Raltitrexed (15-min iv infusion) every 3 weeks on days 1 and 21, and UFT (orally three times a day) on days 1 to 28, followed by 2 weeks' rest of a 6 weeks cycle. The dose limiting toxicity (DLT) was defined as: Diarrhoea grade III; mucositis grade III; platelets grade III; Leukocytes grade IV; Neutrophils gradeIV; Other Toxicity grade II, excluding alopecia or increase transaminases levels.

Results: Since December 1998 to September2000, 33 pts have been enrolled: median age 62.6 (range: 38-71) years; **WHO** performance status:

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.

'Tomudex' is a trademark, the property of the AstraZeneca group of companies

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

G. Masi[1], G. Allegrini[1], S. Cupini[1], L. Marcucci[1], E. Cerri[1], I. Brunetti[2], S. Ricci[2], E. Baldinacci[1], M. Andreuccetti[1], A. Falcone[1]. [1]*Civil Hospital, Medical Oncology, Livorno, Italy;* [2]*S. Chiara Hospital, Medical Oncology, Pisa, Italy*

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

J. Feliu[1], P. Escudero[2], F. Losa[3], M. Bolaños[4], J. Vicent[5], A. Yubero[6], J. Sanz-Lacalle[7], R. López[8], L. López-Gómez[9], M. González-Barón[10]. [1]*Hospital La Paz, Servicio de Oncología Médica, Madrid, Spain;* [2]*Hospital Clínico Lozano Blesa, Servicio de Oncología Médica, Zaragoza, Spain;* [3]*Hospital Cruz Roja, Servicio de Oncología Médica, Barcelona, Spain;* [4]*Hospital San Pedro Alcántara, Servicio de Oncología Médica, Cáceres, Spain;* [5]*Hospital General Universitario de Valencia, Servicio de Oncología Médica, Valencia, Spain;* [6]*Hospital Obispo Polanco, Servicio de Oncología Médica, Teruel, Spain;* [7]*Hospital San Jorge, Servicio de Oncología Médica, Huesca, Spain;* [8]*Hospital Clínico Santiago de Compostela, Servicio de Oncología Médica, Santiago de Compostela, Spain;* [9]*Hospital Virgen de la Salud, Servicio de Oncología Médica, Toledo, Spain;* [10]*Hospital La Paz, Servicio de Oncología Médica, Madrid, Spain*

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

M. Yanagisawa, K. F.-Ouchi, Y. Tanaka. *Chugai Pharmaceutical Co., Ltd., Product Research, Kamakura, Japan*

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-