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A multicenter prospective phase II study of oxaliplatin (OXA), 5-fluorouracil (5FU) and leucovorin (LV) followed, by irininotecan (IRI), 5FU and LV after progression, in patients (pts) with untreated metastatic colorectal carcinoma (MCRC)

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The combinations of OXA or IRI with 5FU-LV are used as standard treatment in pts with MCRC. However, the right sequence in first or second line is not well defined. We developed a multicenter trial in first-line MCRC, with OXA 85 mg/m2, LV 400 mg/m2, 5FU 400 mg/m2 bolus and 5FU 2400 mg/m2 46h continuous infusion, repeated every 2 weeks. Twelve cycles were scheduled. The treatment could be continued in case of clinical benefit. The objective response was evaluated every six cycles. When progression was observed, patients received IRI 180 mg/m2, LV 400 mg/m2, 5FU 400 mg/m2 bolus and 5FU 2400 mg/m2 46h continuous infusion. From August 2001, 86 pts were enrolled in this trial. The main pts characteristics are: median age 62 years (range 28-76), female/male 36%/64%, primary colon/rectum: 68%/32%, performance status 0-1: 90%, prior adyuvant CT: 21%, number of metastatic sites *geq*: 39%, metastatic liver only: 48%. The number of cycles administered were 621 (median number of cycles/patient: 7; range 1-17). There were 82 patients evaluated for toxicity. The most frequent NCI grade * adverse events, by pts were: neutropenia 17%, diarrhoea 3%, nausea and vomiting 4%, asthenia 3%, hand-food syndrome 1%, constipation 1%, neurotoxicity 11%. Grade 2 neurotoxicity was observed in 28 pts (41%). No toxic death took place. Response was evaluated in 60 pts; 2 had a complete response (CR) and 39 had partial responses (PR), with an objective response rate of 68% (CR 3%, PR 65%), a stable disease rate of 15% and a progression rate of 17%. The median time to progression was 9,4 months (95%CI: 7,7-11). Surgical resection of liver metastasis was performed in 5 pts, after partial response. So far, 17 pts have received second line treatment. This regimen is active and has manageable toxicity as treatment in MCRC.

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Site of intracellular expression of beta-catenin influences the outcome in sporadic colorectal cancer

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Background: Stabilisation and nuclear translocation of beta-catenin are suggested to be the early events in the colorectal carcinogenesis. Nuclear accumulation of beta-catenin was associated with high-grade tumour and increased cell proliferation in epithelial cancers. The aim of our study was to correlate the effects of nuclear and cytoplasmic beta-catenin expression in patients with sporadic colorectal cancer cases with clinical outcome.

Method: Immunohistochemistry was performed on 161 histologically proven colorectal cancer cases and were assessed quantitatively.

Results: Out of 161 samples, 139(86.34%) had over expressed beta-catenin either in the nucleus 54(33.54%), cytoplasm 50(31.06%) or both 35(21.74%). Nuclear expression of beta-catenin was significantly associated with well-differentiated tumours (OR=3.14 p=0.015 CI= 1.25-7.87) and early T' stage disease (OR=2.77 p=0.017 CI= 1.20-6.43). Strong cytoplasmic expression was significantly associated with nodal involvement (p=0.054 χ^2 test), liver metastasis (p=0.050 χ^2 test) and a non-significant association with metastasis (p=0.08 χ^2 test). Using Cox's proportional hazard model, we found significant association between strong cytoplasmic expression and advanced Dukes stage disease with reduced survival (HR=1.59 p=0.044 CI= 1.01-2.50). Those with beta-catenin in the nucleus as well as cytoplasm did not show any significant association with clinical parameters. There were no significant associations found between age and overexpression.

Conclusion: We demonstrate for the first time, cytoplasmic expression was associated with poor clinical outcome in colorectal cancer whereas nuclear expression had an opposite effect. These data suggest that the site of expression has a significant impact on the disease progression by acting *via* different pathways.

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Neoadjuvant treatment of metastatic liver disease with raltitrexed and oxaliplatin in colorectal cancer patients

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Background: Surgical resection is the most effective treatment for colorectal (CRC) liver metastases (mets), but only a minority of patients (p) are initially candidates for a potentially curative resection. The promising activity that raltitrexed and oxaliplatin have recently demonstrated prompted us to study the value of the combination as neoadjuvant treatment.

Material and methods: Inclusion criteria: synchronous not operable or metachronous liver mets of histologically proven CRC, adequate haematological, cardiac, renal and liver function, informed consent. Other metastatic sites excluded. Three categories of nonresectable disease were defined: large size, multinodularity, ill location. The same treatment for all p, raltitrexed: 3 mg/m^2 (15 min iv infusion) and oxaliplatin 130 mg/m^2 (2 h iv infusion) every 3 weeks. Re-staging after 3 and 6 cycles with CT and MRI. Liver resection was performed in those p whose disease became resectable. From 02/2001 to 12/2002, 30 p were treated. Median age: 64 y. ECOG PS: 0, 13 p; 1: 17 p, 18/ 12 colon/rectal cancer. Mets: synchronous: 18 p, metachronous: 12p, > 5 cm in maximum size: 10 p, multinodularity: right lobe: 13 p, bilateral: 13p.

Results: The number of courses given was 129 (1-6, median 4), RDI (two drugs): 0.99. *Toxicity* (WHO) included: Anemia grade 1-2: 16p. Neutropenia g.3: 1p. Thrombocytopenia g.3: 1p. Vomiting g. 1-2: 12 p, g. 3-4: 2p. Diarrhoea g. 1-2: 3p, g. 3: 2p. Asthenia g. 1-2: 12 p, g. 3: 4p. Peripheral neuropathy g. 1-2: 16 p, g. 3: 2p. Increased transaminase activity g. 1-2: 9p, g. 3: 2 p. *Overall response* (29 p, 1 p < 3 cycles) RECIST: 44.8% (CI 95% 26.7- 62.9%), 2 p CR (MRI) and 11 p PR. SD: 7 p. PD: 9 p. Nine p (30%) underwent laparotomic surgery, 7 p radically resected (77.8%). Median follow-up: 7.8 m. Median overall survival: 13.3 m. Median time to progression nonresectable group: 5.6 m and resected group: 9.7 m., 5 p remain disease-free.

Conclusions: Our data suggest that neoadjuvant raltitrexed and oxaliplatin enables liver resection in a significant number of patients (30%) with initially unresectable liver metastases, with an acceptable toxicity profile.

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Phase 2 study of CT-2103 in patients with colorectal cancer having recurrent disease after treatment with a 5-fluorouracil-containing regimen

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CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors. CT-2103 exposes normal organs to conjugated paclitaxel, which is non-toxic in vitro, thus minimizing overall toxicity. CT-2103 showed enhanced efficacy compared to paclitaxel/Cremophor in syngeneic and xenogeneic in vivo tumor models including colorectal tumors and other paclitaxel-resistant cell lines. Conjugation of paclitaxel to poly-L-glutamate enhances aqueous solubility and eliminates the need for Cremophor, resulting in a convenient 10 min infusion. Patients enrolled in the 1st cohort of this multicenter study were heavily pretreated with advanced, measurable colorectal cancer that was resistant to 5-FU/leucovorin. Patients received a conjugated paclitaxel dose of 210 mg/m^2 CT-2103 as a 10 minute IV infusion every 21 days. NCI CTC (v 2) are used for safety assessments. Efficacy was assessed after every 2nd cycle according to RECIST. Sixty patients have been treated. The median age was 63 years (range 34-84) and 60% of patients were male. The median time from diagnosis to start of CT-2103 treatment was 20 months (range 2-94). Fifty-four patients (90%) had received prior CPT-11 and 45 of these patients received CT-2103 <6 months after completing CPT-11 therapy. 87% of patients received 2 or more

cycles of CT-2103. 28% received 3 or more cycles and 15% of the patients received 4 or more cycles. Sixteen patients (27%) had stable disease, 4 of these lasted 6 cycles and 1 lasted 8 cycles. Median time to progression was 40 days. The Kaplan-Meier estimate of survival at 1 year is 23% with a median overall survival estimate of 5.4 months. Clinically significant grade 3/4 drug-related adverse events were limited to febrile neutropenia (4 patients) , stomatitis (4), peripheral neuropathy (2), drug hypersensitivity (1), and sepsis (3). These data suggest that CT-2103 has activity in heavily pretreated patients with 5-FU-resistant advanced colorectal cancer, a tumor not responsive to paclitaxel treatment. Based on these encouraging results, enrollment in this study continues at a higher dose of 235 mg/m^2 in patients with less than 3 prior regimens.

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Promising activity with capecitabine and mitomycin C (MMC) as third line therapy for patients with metastatic colorectal cancer (MCRC) resistant to fluorouracil (5-FU) and irinotecan: results of a phase II study

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Background: Protracted venous infusion 5-FU with MMC has demonstrated significant activity for treatment of MCRC. Due to potential synergy based upon up-regulation of thymidine phosphorylase by MMC and different toxicity profiles, the combination of capecitabine and MMC may improve results in MCRC.

Purpose: To evaluate the safety and efficacy of capecitabine in combination with MMC as third line therapy in MCRC resistant to 5-FU and irinotecan.

Patients and Methods: An optimal 2-stage phase II study design was utilised. Eligibility criteria included WHO performance status (PS) 0-2, the ability to take oral medications and adequate haematological, renal and hepatic function. All patients (pts) demonstrated progressive disease (PD) whilst receiving chemotherapy or within 6 months of cessation of treatment. Capecitabine (1250 mg/m2 PO BD) for 14 days followed by 7 days break, every 3 weeks and MMC (7 mg/m2 IV bolus) once every 6 weeks was given. CT response assessment was performed at 12 and 24 weeks.

Results: Between 7/01 and 12/02, 31 pts were recruited, with 17 (55%) males, median age of 64 years (range 40-77) and 23 (74%) were PS 0-1. Sites of metastatic disease were liver (74%), lung (35%), peritoneum (16%), lymph nodes (13%) and omentum (6%). 15 pts (48%) had $\geq$ 2 sites of metastatic disease. The overall response rate for the 23 evaluable pts was 22% (95% CI: 6.8-40.7%). In addition, 13 pts (57%) had stable disease. Grade 3/4 toxicities were hand foot syndrome 23%, vomiting 11.5%, diarrhoea 3.9%, anaemia 7.4%, and neutropenia 3.7%. No pts developed haemolytic uraemic syndrome. Symptomatic improvement was noted for pain (85%), bowel symptoms (86%) and dyspnoea (100%).

Conclusion: Capecitabine in combination with MMC shows promise for MCRC resistant to 5-FU and irinotecan in terms of efficacy, acceptable toxicity profile, symptom control and ease of administration. Stage II recruitment is ongoing in accordance with the study design.

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Combination of irinotecan and capecitabine as first line treatment in advanced colorectal cancer (ACC): results of a phase II multicenter trial.

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Background: irinotecan (iri) in combination with intravenous (iv) 5-Fluorouracil (5-FU) and folinic acid (FA) either weekly bolus or biweekly infusional is an effective first-line treatment in patients (pts) with ACC. Capecitabine (cap) is an oral fluoropyrimidine with comparable efficacy to 5FU/FA in this setting. In a previous phase I study the recommended dose of the combination was cap 1000 mg/m^2 twice daily, day 1 14, and iri 250 mg/m^2, starting 2 hours after cap, day 1 i.v. 30 minutes, q 3 weeks (*Kerr et al. Proc. ASCO 2002 abstr. 643*). Tumour response rate was promising. The reverse sequence (iri followed 2 hours later by cap) was assessed in phase II study at the recommended dose. These results (*Falcone et al. J Clin Oncol 2001)* suggest an improved safety profile for this sequence. After evaluation of the safety of the first 3 cycles of the first 15 pts, 42 additional pts were included.

Material and methods: Treatment plan: iri 250 mg/m^2 mg i.v. over 30 minutes, day 1, q 3 wks and cap, 1000 mg/m^2 orally twice daily 12 hours apart from d1 to d14, q 3 wks, with the first dose of cap being given 2 hours after iri. Efficacy and safety were evaluated.

Main eligibility criteria: no prior systemic treatment for advanced disease, measurable disease, WHO performance status $\leq$ 2, adequate haematological, hepatic and renal function. Prior adjuvant chemotherapy was allowed if completed more than 6 months ago.

Results: Patients characteristics: 34 male and 23 female, median age 60 years, 41 pts PS 0, 16 pts PS 1. Primary tumour: colon 33 rectum 15 and rectosigmoid 9. Median number of metastatic sites 2. Prior adjuvant chemotherapy 16. Safety analysis in the 1st cohort of 15 pts revealed grade 3-4: diarrhea 3 pts, nausea 1 pt, vomiting 1 pt, hand-foot syndrome 1 pt, neutropenia 3 pts, infection with neutropenia 1 pt, pain 2 pts, fatigue 1 pt, and 1 patient experienced coronary vein spasm grade 2 in first cycle.

Conclusion: The preliminary response assessment after 12 weeks therapy show a corrective response. Results on efficacy and safety for the total population as well as pharmacokinetic analysis will be presented at the meeting. Currently this schedule of iri/cap is being tested in randomized trials in ACC.

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Functional status during and after adjuvant therapy for colorectal cancer.

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Our objective was to evaluate the impact of adjuvant therapy for colorectal cancer on physical function and other functional domains of health-related quality of life.

Methods. Patients completed the EORTC QLQ-C30 core questionnaire and CR38 colorectal module, maximal handgrip strength (HG), and other measures prior to, during, and at the completion of therapy, and 6 months later (follow-up).

Results. One hundred and fifty patients have been enrolled to date, age range 35-79 years, mean 62 years. Physical function (PF) improved minimally during therapy ($P<0.05$) and was similar to baseline at follow-up. Role function (RF) improved moderately during therapy and follow-up ($P<0.001$). Cognitive function (CF) declined to a minor extent during therapy ($P<0.05$), but was similar to baseline at follow-up. Emotional function (EF) improved to a minor extent ($P<0.05$) and social function (SF) to a moderate extent ($P<0.001$) during therapy and follow-up. Global health status did not change during treatment, but was greater at follow-up than baseline ($P<0.05$). Future perspective increased moderately with commencement of therapy and remained higher at followup ($P<0.001$). Fatigue did not change from baseline during therapy but was lower at follow-up than baseline ($p<0.001$). Baseline HG was inversely related to age and was lower in women ($r^2=0.57$, all $P<0.001$). HG increased from baseline to follow-up ($P<0.05$). Age-related differences in function were modest: RF decreased moderately during therapy in patients aged 65 or older ($P<0.01$, n=65), but recovered subsequently, whereas RF improved throughout in younger patients ($P<0.01$, n=85). Differences between patients with colon and rectal cancer and between men and women were minor.

Conclusions. The functional impact of adjuvant therapy for colorectal cancer is limited. Global health status and self-reported function in all domains were maintained or improved during adjuvant therapy, with the exception of transient, minor impairment in cognitive function. Moreover, at six months following adjuvant therapy, function in all domains was similar to or better than baseline. The limited impact of adjuvant therapy may reflect recovery from baseline impairments in some domains related to recent major colorectal resection. This information is of value for clinical decision-making and defining social support needs, and may identify predictors of individuals sustaining significant impairments.