a large number of SNP's based on analysis of individual samples is time consuming and expensive.

**Materials and methods:** We have established a pooling strategy for detection of SNP's in genes, which are known in the pathogenesis of colorectal cancer, including APC, beta-catenin, E-cadherin, K-ras, p53 and others. The SNP's are selected from the dbSNP-NCBI database (). We have constructed pools of DNA from 230 patients with diagnosed sporadic colorectal cancer and from 540 controls. 100 ng. of genomic DNA from each individual is used for the pool. The pool holds DNA for approximately 1500-2000 individual SNP analysis.

The method involves PCR amplification of genomic DNA fragment including the SNP, single base extension (SBE) reaction of SNP using fluorescent-labelled ddNTP followed by capillary electrophoresis of single base reaction products.

We aim at screening 500 SNP's for association with disease development covering approximately 50 genes.

**Results:** SNP's are screened by analyzing frequency in case-pool and in control-pool. SNP's showing a minor allele frequency of >10% are further analyzed, and candidates showing difference in allele frequency between the two pools are further validated by sequencing.

**Preliminary results screening 63 SNP's in 7 genes show:**

Positive PCR product Positive SBE product Minor allel frequency >10% Non conclusive data

60/63 = 95% 59/61 = 97% 25/61 = 41% 2/61 = 3%

The total number of single reactions for screening of the 63 SNP's in pools is 704 as compared to 48.510 reactions by analyzing individual samples, thereby reducing the number of analysis by a factor of 69.

**Conclusions:** We have established a method for screening of large number of SNP's in genes suspected for a potential role in development of sporadic colorectal cancer. The method significantly reduces the total number of reactions and the amount of DNA used for SNP analysis, as compared to analysis of individual samples, and identifies SNP's suspected for association with disease development.

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## Effects of capecitabine (Xeloda) on quality of life (QoL) in patients with metastatic colorectal cancer (MCRC)

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**Background:** While outcomes such as objective response, time to disease progression and overall survival are well-established measures of treatment response, the QoL benefits of oral treatments, such as the novel fluoropyrimidine capecitabine (Xeloda®), are important when choosing appropriate therapy for MCRC.

**Patients and Methods:** QoL was assessed in a sample of 209 patients receiving oral capecitabine as second- or third-line therapy for MCRC. Patients completed the EORTC QLQ C-30 questionnaire and the specific model for colorectal cancer (CR-38) at baseline, before the first cycle of treatment, at weeks 7 and 13, and at the end of treatment. Linear models with repeated measures of the scores were used to analyse questionnaire responses over time. The proportion of patients with an improvement, stabilisation or worsening of QoL scores from week 7 onwards was analysed with generalised linear models for repeated measures, using the generalised estimating questions technique. Statistical analysis was performed using an SAS programme (system version 8.2).

**Results:** Patient characteristics were as follows: male/female, 54.5%/45.5%; mean age 53.9 years (range 25.0-72.0 years); white/Caucasian, 89%. Almost 50% of patients completed the questionnaires at all time points. Variables for which a statistically significant improvement in QoL over time was detected included global health status (p=0.04), physical functioning (p=0.04), financial problems (p=0.008), future perspective (p=0.006) and weight loss (p=0.0008). The proportion of patients that remained stable or improved was * 70% for most scales. At least 30% of patients reported improvements in the following QoL scales from week 7 onwards: global health status (38%); social functioning (36%); fatigue (36%); pain (35%); micturition problems (33%); role functioning (31%); emotional functioning (31%); future perspective (31%); chemotherapy side-effects (31%). After all time points *"at the end of treatment?"*, 46% of patients showed an improvement in global health status and 24% had stable scores. In addition, 45% of the total number of patients experienced improvement in fatigue and 43% had improvement in social functioning.

**Conclusion:** These findings indicate that the efficacy, safety and convenience of capecitabine allow patients to maintain a normal lifestyle and have a direct impact on QoL. This important measure should be considered along with established treatment outcomes when deciding on patient therapy in MCRC.

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## Peritoneal carcinomatosis of colorectal origin: results of palliative surgery and systemic chemotherapy.

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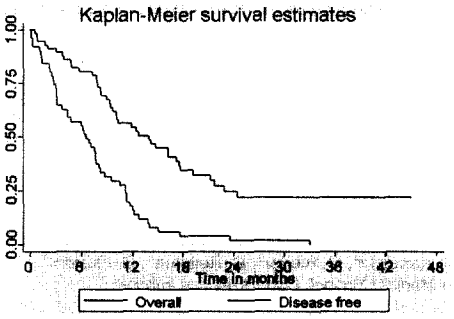
**Back ground:** Peritoneal carcinomatosis (PC) has a grave prognosis. New treatments like extensive surgical resection and intra-peritoneal chemotherapy may enhance survival. This novel treatment seems to create an improved survival in patients with PC of CRC origin without distant metastasis. Very little is known about the results of systemic chemotherapy in these patients.

**Methods:** 57 patients with proven peritoneal carcinomatosis of colorectal origin without distant metastasis treated with palliative surgery and fluorouracil (5FU)(400mg/m$^2$) and folinic acid (80mg/m$^2$) once weekly, or irinotecan (CPT 11) (350mg/m$^2$) every three weeks in patients treated with 5FU within 12 months prior to study entry were studied. The median follow-up was 40 months (range 2.5 - 62 months). The following prognostic factors were analysed: gender, location of primary CRC, PC at diagnosis CRC or recurrent CRC and palliative resections. Analysis: Survival and progression free survival was calculated by the Kaplan Meyer method. Prognostic factors where analysed using the log-rank test.

**Results:** The median survival of peritoneal carcinomatosis was 14.1 months when treated by palliative surgery and systemic chemotherapy. Median progression free survival was 7.7 months. Kaplan Meyer curves are shown in the figure Female gender correlate with improved survival, but this did not reach significance (p=0.0741). Patients in whom a resection was possible had a significant better prognosis (improvement from 8.3 to 17.3 months (p=0.0042)). None of the other factors were related to survival.




**Conclusion:** Survival of PC of CRC origin is poor when treated by palliative surgery and systemic chemotherapy only. If a palliative resection is possible the survival significantly improves probably related.

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## Equal prognosis of elderly and non-elderly patients with metastatic colorectal cancer and 5-FU treatment: a retrospective analysis.

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**Introduction:** There is, uncertainty as to what extent systemic adjuvant or palliative chemotherapy should be offered to elderly patients with colorectal cancer. This fact is related to the unfortunate underrepresentation or even

exclusion of fit elderly patients from clinical studies and also to the total lack of studies in unfit elderly, who represent at least 50% of the geriatric population presenting into major hospitals.

**Methods:** We analysed a database of 3825 patients treated within different European trials for the prognosis of elderly (> 70 years, n= 711) and non-elderly patients (<= 70 years, n=3114).

**Results:** There was a difference in the percentage of elderly patients included in the different European countries: the highest rate in Austria (38%) and lowest in the UK (3%), Germany had 13% and overall 19% of patients were above 70 years of age. The distrubution of age groups was as follows: 70-75 years 370 pts, 75-80 years 116 pts, > 80 years 20 pts (only 1 patient above 85 years). Elderly patients had a higher incidence of rectal primary (p=0.01), more frequent weight loss (p=0.03) and more prior adjuvant chemotherapy (p<0.0001). Significant prognostic factors (Köhne et al. ASCO 2000) like WBC, thrombocytosis, alkaline phosphastase and LDH all were in favour of elderly patients, however the distribution into good (52% vs. 73%), intermediate (27% vs. 26%) or poor risk (21% vs. 21%) of non-elderly and elderly patients did not differ significantly. Objective responses were more likely to occur in elderly patients (26% vs. 21%, p=0.005). Relapse free survival (5.3 vs. 5.8 months, p<0.0001) and overall survival (11.1 vs. 12.0 months, p<0.001) were all in favour of elderly patients with insignificant clinical albeit statistical significance. Survival of elderly vs. non-elderly patients in the three previously defined risk groups did not differ. Older age was also not an independent prognostic parameter.

**Conclusions:** Fit elderly patients should not be excluded from clinical trials and studies in unfit elderly patients are warranted and currently discussed by The International Society of Geriatric Oncology (SIOG) and DGHO elderly group. Elderly patients need more attention regarding their functional, social and mental status.

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## Capecitabine plus oxaliplatin (XELOX): findings from a human colon cancer xenograft model and a phase II clinical trial in patients with metastatic colorectal cancer (MCRC)

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**Background:** Capecitabine (Xeloda®, an oral tumoractivated fluoropyrimidine, is replacing i.v. 5-FU as first-line therapy in MCRC based on its high single-agent activity (response rate [RR] 26%) and improved safety compared with bolus 5-FU/LV. With other advantages in terms of convenience and patient preference for oral therapy, capecitabine could also replace i.v. 5-FU in combination regimens. Adding oxaliplatin (single agent RR approx. 10%) to infused 5-FU/LV improves efficacy in patients with MCRC. Since capecitabine and oxaliplatin have key toxicities that do not overlap, capecitabine is an attractive combination partner for oxaliplatin.

**Preclinical Study:** The antitumor activity of XELOX was evaluated in mice with CXF280 human colon cancer xenograft. Capecitabine was administered p.o. on days 1-14 plus oxaliplatin i.v. on day 1, every 21 days. Combining capecitabine and oxaliplatin produced at least additive antitumor activity. XELOX at two-thirds of the maximum tolerated dose (MTD) for each agent was more potent than either single agent at their MTD. Furthermore, oxaliplatin upregulated the tumor level of thymidine phosphorylase (TP), the final enzyme in the conversion of capecitabine to 5-FU. This upregulation of TP by oxaliplatin was not observed in two further colon cancer xenograft models that were unresponsive to oxaliplatin.

**Phase II Clinical Study:** 96 patients (61 men, 35 women) received i.v. oxaliplatin (130 mg/m$^2$, day 1) plus oral capecitabine (1000 mg/m$^2$, twice daily on days 1-14) every 21 days as first-line treatment for MCRC. Median age was 64; colon cancer (63%)/rectal cancer (33%)/both (4%); 54% had >1 metastatic site; 77%, 39% and 32% had liver, lymph node or lung metastases, respectively; 28% had received adjuvant fluoropyrimidines. All patients were evaluable for efficacy and safety. RR was 55% (95% CI, 45-65%) and 31% of patients had SD >3 months. Median TTP was 7.6 months (95% CI, 6.4-8.6 months) and median overall survival was 19.5 months. Grade 3/4 toxicities were sensory neuropathy (16%), diarrhea (16%), nausea/vomiting (13%), asthenia (9%), neuropathic pain (6%), neutropenia (7%), and thrombocytopenia (4%). Grade 3 hand-foot syndrome affected only 3% of patients and 60-day all cause mortality was 2.1%.

**Conclusions:** The clinical findings (RR 55% and good tolerability) confirm the preclinical observations in human colon cancer xenografts and indicate that XELOX is a highly active and appropriate first-line treatment for MCRC.

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## Capecitabine plus irinotecan (XELIRI) in first line metastatic colorectal cancer (MCRC): update on a phase II trial

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**Background:** Capecitabine (Xeloda®), a tumor-activated oral fluoropyrimidine, has superior activity and an improved safety profile compared to 5-FU/LV in 1st line MCRC. Adding irinotecan (CPT) to bolus or infused 5-FU/LV improves efficacy, but safety appears better with infused 5-FU. However, infused combinations are burdensome and time-consuming for patients and healthcare providers alike. Mimicking infusion with twice-daily oral administration, capecitabine can replace infused 5-FU in combination therapy. The combination of capecitabine (X) and CPT should be an effective, safe, and more convenient 1st line option.

**Materials and methods:** Recommended doses were identified in 2 independent phase I trials [1]: intravenous CPT (250 mg/m$^2$ d1) followed by intermittent oral X (1000 mg/m$^2$ twice-daily for 14 days) every 3 weeks, from evening day 1 to morning day 15. To improve safety and permit treatment of older patients (pts), those ≥ 65 years old received lower doses of both agents (200/750). Objectives were to evaluate efficacy and safety in 1st line MCRC pts.

**Results:** Accrual is complete (n=52). 51 patients are evaluable for safety and 43 for response: 29 men (56%), 23 women (44%); median Karnofsky PS 90 (70-100), median age 57.5 (30-79). 44 pts (85%) had colon cancer, 6 rectal (11%) and 2 both (4%). Tumor differentiation was 15% poor, 64% moderate, 11% well and 10% unknown. 41 pts (79%) had liver metastases and 31 (60%) had stage IV disease at initial diagnosis. 10 pts (19%) received prior adjuvant 5-FU. Median number of treatment cycles is currently 5 (70% ≥ 4 cycles, 44% ≥ 6, 14% = maximum of 12 cycles) with a median follow-up of 39 weeks (range, 11 to 68 weeks). Most common (>5%) AEs (all grade 3) were diarrhea 22%, nausea/vomiting 12%, dehydration 12% (1 pt with grade 4), hand-foot syndrome 6%. Grade 3 or 4 neutropenia was seen in 18%. There were no treatment-related deaths. Response rate was 18/43 (42%) with another 17 stabilizations (39%, including 8 unconfirmed responses, giving tumor control in 8/10 patients). In one center, 8 patients were able to undergo potentially-curative resection following their chemotherapy. Median time to progression (TTP) is currently 6.4 months (range, 1-13).

**Conclusion:** X should replace 5-FU in combination with CPT to create an effective, safe, and less burdensome treatment option in 1st line MCRC. XELIRI compares favorably with standard CPT/5-FU/LV combination regimens in terms of response rate and TTP. Updated results will be presented.

### Reference

[1] Kerr et al, Delord et al. ASCO 02 abstracts 643 & 397

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## Twelve weeks of neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation (CRT) and total mesorectal excision (TME) in MRI defined poor risk locally advanced rectal cancer resulted in promising tumour regression and rapid symptomatic relief

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**Purpose:** To evaluate neoadjuvant capecitabine/oxaliplatin prior to CRT and TME in newly diagnosed patients with MRI defined poor risk/locally advanced rectal cancer. Patients and Methods: MRI criteria for poor risk rectal cancer were: tumours within 2mm of mesorectal fascia i.e. circumferential resection margin (CRM) threatened; T3 tumours at/below levators; tumours extending more than or equal to 5mm into peri-rectal fat;