Results: *Patients characteristics*: 64 pts treated; median age: 68 years (range: 38-81); ECOG PS 0,1: 63%, 37%; 36 males; tumor sites: colon 60%, rectum 23%, junction: 17%; liver metastasis 80%; prior treatment: surgery 94%, (neo) adjuvant chemotherapy: 27%, radiotherapy: 14%. *Safety:* A total of 347 cycles (median: 6; range: 1-14) were given. To date, safety has been evaluated in 47 pts. Adverse reactions per patient were G3 diarrhea: 15%; G3 nausea/vomiting: 9%; G2 sensory neuropathy: 26%; neutropenia: 8%. *Efficacy:* Objective Responses were reviewed by an independent panel of expert radiologists on the 64 patients included. One patient was non evaluable for response, 5 patients did not undergo tumor assessment for early withdrawal from the study. Among the 58 evaluable patients, responses were as follows: CR: 1 pt, PR: 18 pts, ORR: 32.7% (95% CI 21-45) with 42% stable disease. TTP and survival results will be presented at the meeting.

Conclusion: Tegafox is an effective regimen with an acceptable tolerance. This regimen should be compared to Oxaliplatin with i.v. 5FU/LV in patients with metastatic CRC. Supported by Bristol-Myers Squibb, France

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Raltitrexed (Tomudex) combined with UFT: a final results phase II study in patients with advanced colorectal cancer (ACRC).

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Aims: A Preliminary dose-escalation trial confirmed that recommended dose for the combination of Tomudex (TOM) and UFT are TOM 3 mg/m^2 and UFT 350 mg/m^2.

The primary aim of this study is to assess the efficacy and tolerability of TOM and UFT combination in patients (Pt) with ACRC.

Patients and Methods: Inclusion criteria: Advanced Colorectal Adenocarcinoma, aged $\geq$ 18 years $\leq$ 75, WHO performance status score $\leq$ 2, satisfactory haematological, renal and hepatic function, and at least one assessable or measurable lesion. TOM 3 mg/m^2 was administered as a 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. All Pt who received at least one cycle were evaluated for toxicity and those who received more than 2 cycles were evaluated for efficacy. Response was assessed by imaging techniques and categorised according to UICC Criteria.

Results: From January 2000 to June 2002, 36 Pt were included in 4 Spanish centres. Mean age was 63.6 years (range:44-75). The ECOG at inclusion was: 0 in 8.3%; 1 in 80.6% and 2 in 11.1%. The most common metastases locations were: liver 29 (80.6%), lung 6 (16.7%), and lymphatic node 2 (5.56%). A total of 10 Pt showed 1 metastatic site (33.3%). Another 14 showed 2 metastatic sites (38.9%) and the remaining 12 showed 3 or more metastatic sites (27.8%). A total of 199 Raltitrexed doses were administered, median 5 per patient (range: 1-16). Moderate/severe toxicity grade III-IV was assessed: Neutropenia 11 (30.6%), diarrhoea 8 (22.2%), nausea 3 (8.3%). Efficacy results: Two Pt had a complete response and 10 a partial response, Overall Response 33.3% (C.I.95%: 18.6%-51.0%); 41.7% had stable disease, 8,3% had progressive disease, and 16,6% were non valuable due non-assessment. Median time to progression 26.1 weeks.

Conclusions: Tomudex plus UFT combination is an active treatment in ACRC, obtaining a good objective response percentage, 33.3% and a high percentage disease control, 75.0%. Toxicity is moderate, *neutropenia* being the most frequent event reported.

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Tissue inhibitor of metalloproteinase 3 (TIMP-3) is a new putative target gene in colorectal carcinomas with microsatellite instability (MSI)

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Background/Aim: Microsatellite instability (MSI)is the phenotype of colorectal cancer with a DNA mismatch repair deficiency. Genes with repetitive elements in their coding sequence (CDS) might be target genes for mutations in MSI+ cases. In this study the TIMP-3 gene with a C7 repeat in its CDS was screened for frameshift mutations in colorectal carcinomas. Additionally, the TIMP-3 promotor was analysed for CpG island hypermethylation.

Material/Methods: 40 MSI+ tumours, 20 MSI- cases and 6 cell lines, all previously characterised for MSI status, were selected for this study. The exon 5 of the TIMP-3 gene containing the C7 repeat was analysed for gene mutations using fluorescence PCR followed by capillary electrophoresis. All cases presenting with band shifts in the PCR were sequenced. Additionally, the TIMP-3 promotor was analysed using bisulfite treatment followed by CpG island amplification.

Results: A frameshift mutation could be found in 3 MSI+ tumours and in a colon cancer cell line (SW48). The detected mutations consisted of two insertion-mutations (C8) and two deletion-mutations (C6), respecitely, leading to quantitative and qualitative peptide changes 3' behind the mutation, a region highly conserved during evolution. Additionally, TIMP-3 promotor hypermethylation was present in 2 cell lines and in 11 of 40 (27%) MSI+ tumours.

Conclusions: It could be shown, that the TIMP-3 gene is mutated or methylated in about one third of MSI+ colorectal carcinoma studied. Therefore, it represents a putative new target in tumours of the "mutator-pathway". In combination with recently published data about involvement of MMP-3 and MMP-9 in MSI+ colorectal tumours one might conclude that the family of matrix-metalloproteinases might be of importance for carcinogenesis in the DNA mismatch repair deficient pathway.

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Capecitabine plus irinotecan (CAPIRI) vs capecitabine plus oxaliplatin (CAPOX) as first-line therapy of advanced colorectal cancer (ACRC): updated results of a randomized phase II trial

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Background To assess combining capecitabine (CAP) with irinotecan (IRI) or oxaliplatin (OX) as first-line therapy in ACRC, we performed a randomized phase II trial comparing CAPIRI with CAPOX with optional cross-over after failure of first-line treatment.

	CAPIRI	CAPOX	p-value
N pts	67	75	
Overall response rate (%) (95% CI)	40.3 (28.5-53.6)	50.7 (38.9-62.4)	n.s.
CR (%)	3.0	6.7	
PR (%)	37.3	44.0	
SD (%)	41.8	41.3	
PD (%)	17.9	8.0	
Progression-free survival (months) (95% CI)	7.9 (5.4-9.2)	7.2 (5.7-10.1)	n.s.
% Censored pts	33.3	42.0	
Overall survival (months)	NA	NA	
% Censored pts	67.1	67.9	

Materials and methods: CAP 1000 mg/m2 twice-daily d1-14 plus IRI 100 mg/m2 iv d1, 8 or OX 70 mg/m2 iv d1, 8; q3w. 161 patients (pts) were randomized (median age 63 (33-77), m:f 113:48, CAPIRI 79, CAPOX 82, both arms balanced for age, sex, prior adjuvant, location of primary tumor, number of metastatic sites); 160 pts (CAPIRI 79, CAPOX 81) are evaluable for safety, 142 pts (CAPIRI 67, CAPOX 75) for efficacy. Results from cross-over are currently available for 46 pts.

Results: NCI-CTC grade 3/4 toxicities were equally frequent in both treatment arms (CAPIRI vs CAPOX: diarrhea 12.7 vs 13.6%, nausea/vomiting 6.3 vs 3.7%, infection 3.8 vs 4.9%, cardiac 1.7 vs 1.5%, thrombosis 1.7 vs 1.5%, sensory neuropathy 1.3 vs 6.2%, bilirubin 7.7 vs 7.4%. Four of the first 40 pts in the CAPIRI arm died within the first 60 days after onset of therapy due to septic diarrhea in neutropenia (1 pt), pulmonary embolism (2 pts), and unknown cause (1 pt); subsequently the IRI dose was reduced to 80 mg/m2 d1, 8. Overall, 60-day all cause mortality was 6.3 vs 1.2% (p=n.s.). Preliminary efficacy parameters are detailed in the table below. Dose reduction of IRI did not affect efficacy of CAPIRI. In interim analysis, second-line CAPIRI (CAPOX) achieved CR/PR in 19 (12%) and SD in 47 (44%) of pts.

Conclusions: CAPIRI and CAPOX show substantial efficacy in ACRC. Toxicity profiles are similar with the exception of a higher incidence of early deaths in the CAPIRI arm in the first phase of the trial. Capecitabine appears

to be an acceptable alternative to infusional 5-FU/LV in combination therapy. Updated results including data on second-line treatment will be presented at the meeting.

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Microarray expression analysis indicates a central role for matrix-metalloproteinases MMP-1, MMP-3, MMP-9 and TIMP-3 in the metastatic process of colorectal carcinomas

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Background/Aims: To date, the molecular basis of the metastatic process is understood only by part. However, the family of matrix-metalloproteinases seems to be involved due to their ability to degrade the extracellular matrix, to induce angiogenesis and to influence apoptosis. In this study the gene expression profile of colorectal carcinomas and their corresponding liver metastases were analysed using gene-expression microarrays to get a deeper view of the genes and pathways involved in metastasis.

Material/Methods: After written informed consent tumour material from nine colorectal primaries and biopsies from the corresponding liver metastases were taken intraoperatively and immediately snap-frozen in liquid nitrogen. The tissues were laser-microdissected, amplified and hybridised to Affymetrix U-133A microarrays according to the manufacturers instructions. 18 gene expression datasets comprising 22,283 human genes and ESTs each were analysed for statistic significance between colorectal carcinomas and liver metastases Results were verified by RT-PCR.

Results: The gene-expression for MMP-1, MMP-3, MMP-9 and TIMP-3 was statistically significant increased in colorectal carcinomas in contrast to liver metastases. Additionally changes in gene expression could be detected for collagens I, III, V, X, laminin, heparansulfate, transmembrane-4 family members and tetraspan. Furthermore, expression changes were obvious for genes involved in angiogenesis, e.g. the endothelin receptor or the plasminogen activator. The increased expression of MMP regulatory genes (CDC42, RAS and FOS) confirm the hypothesis for the involvement by this pathway.

Conclusions: Using genome-wide gene expression analysis we could show a central role for MMP-1, MMP-3, MMP-9 and TIMP-3 in the metastatic process in vivo. Further potential candidates with significant expression differences between primary and metastatic tumours are profen for relevance at present.

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Preliminary phase I results of the oral, once-daily angiogenesis inhibitor PTK787/ZK 222584 (PTK/ZK) in combination with chemotherapy for the treatment of metastatic colorectal cancer

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Background: PTK/ZK is a novel, oral angiogenesis inhibitor that potently inhibits the vascular endothelial growth factor receptor-1 and -2 tyrosine kinases, important receptors contributing to new blood vessel formation during tumor growth and metastasis. Daily administration of PTK/ZK, alone and in combination with chemotherapy, has been generally well tolerated in more than 450 patients, and PTK/ZK significantly reduced tumor blood supply with associated significant reductions in the size of colorectal cancer liver metastases.

Material and Methods: This study assessed safety and preliminary efficacy of PTK/ZK in combination with 2 different chemotherapy regimens. Previously untreated patients with measurable, advanced-stage colorectal cancer were treated with oral PTK/ZK plus either oxaliplatin/5-fluorouracil (5-FU)/leucovorin (FOLFOX4) or irinotecan/5-FU/leucovorin (FOLFIRI) in a phase I/II, dose-escalation study. PTK/ZK was administered at doses ranging from 500 to 2,000 mg/day. Oxaliplatin (85 mg/m^2) or irinotecan (180 mg/m^2) was administered on day 1, and leucovorin (200 mg/m^2 via 2-hour infusion) and 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 via 22-hour infusion) were administered on days 1 and 2 every 2 weeks. Tumor response was assessed every 12 weeks.

Results: To date, 35 patients have been treated with PTK/ZK plus FOLFOX4, and 16 patients have received PTK/ZK plus FOLFIRI. Both combinations were generally well tolerated. In the FOLFOX4 arm, lightheadedness and dizziness were dose limiting at 2,000 mg/day PTK/ZK; the maximum tolerated dose has not yet been reached in the FOLFIRI arm (with dosing currently at 1,250 mg). Preliminary results suggest that PTK/ZK did not affect the safety profile of either chemotherapy regimen or alter the pharmacokinetics of oxaliplatin. Among 21 evaluable patients treated with PTK/ZK + FOLFOX4, 9 (43%) had a partial response (PR), 8 (38%) had stable disease, and 4 (19%) had progressive disease. For 29 patients to date, median time to progression is 10.8 months (95% CI, 6.9-13.4 months). Among 9 evaluable patients treated with PTK/ZK + FOLFIRI, 4 (44%) had a PR and 5 (56%) had stable disease.

Conclusions: These preliminary results suggest that PTK/ZK combined with FOLFOX4 and FOLFIRI is feasible and well tolerated. The results are promising, particularly with regard to time to progression, and patients continue to be accrued to this trial.

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Comparison between radiotherapy and neoadjuvant chemotherapy and radiotherapy in a population based series of epidermoid anal carcinomas

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Background: Primary treatment of epidermoid anal cancer is radiotherapy (RT) alone, or in combination with chemotherapy. Radical surgery is reserved for poor responders or recurrences. The use of concomitant chemoradiotherapy as well as neoadjuvant chemotherapy followed by RT has been reported in the literature. This study presents results from a large population-based material and provides comparison between different treatments.

Material and methods: Between 1985 and 2000, 308 patients with invasive epidermoid anal cancer were diagnosed in the Stockholm Health Care Region. All patients were prospectively recorded. Treatment was given according to defined protocols. Between 1985 and 1991 RT+/-concomitant bleomycin was used for all tumours. Between 1989 and 2000 patients with locally advanced tumours (T>4 cm or N+) received neoadjuvant platinum based chemotherapy followed by RT, whereas smaller lesions were treated with RT alone.

Results: Among the 276 patients (90%) who were treated with curative intent, 264 (96%) received treatment in accordance with the protocols. Among 142 patients with locally advanced tumours treated with either RT+/-concomitant bleomycin (n=51) or neoadjuvant platinum based chemotherapy and RT (n=91), the complete response rate (CR) was 87%. Patients receiving neoadjuvant chemotherapy had a significantly higher CR-rate compared to those treated with RT+/-bleomycin (92 vs. 76%, p<0.01). The overall 5-year survival rate among patients with locally advanced tumours was 59%. A significantly higher 5-year survival rate was found in the neoadjuvant group (63 vs. 44%, p<0.05). Isolated locoregional failures, either as residual tumour after completion of therapy or as recurrences, occurred significantly more frequent among patients receiving RT+/-bleomycin (31 vs. 14%, p<0.05). Multivariate analyses revealed treatment as an independent prognostic factor.

Conclusions: The results suggest that neoadjuvant platinum based chemotherapy and RT is superior to RT alone or with bleomycin in the treatment of locally advanced cases of epidermoid anal cancer. For confirmation of superiority to the present reference regimen, being RT with concomitant 5-FU and mitomycin C (or cisplatinum), a randomised trial is needed.

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Screening for single nucleotide polymorphism (snp) in association with sporadic colorectal cancer.

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Background: The cumulative life time risk of developing sporadic colorectal cancer (CRC) in the Western Europe is approximately 6%. A first-degree relative to patients with sporadic CRC is twice as likely to develop the disease. We believe that single nucleotide polymorphism (SNP) may be important for susceptibility for disease development. However screening of