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