Results: Patients characteristics were (arm A vs arm B): median age 64 vs 62 yrs, ECOG PS 1–2 40% vs 39%, adjuvant CT 24% vs 24%, multiple sites of metastasis 48% vs 55%, liver metastases 79% vs 75%, liver involvement ⩾25% 58% vs 52%. Main observed toxicities were (arm A vs arm B): grade 3–4 diarrhea 12% vs 18%, grade 2–3 vomiting 20% vs 31%, grade 3–4 stomatitis 3% vs 5%, grade 2–3 peripheral neurotoxicity 0% vs 20%, grade 4 neutropenia 28% vs 47%, febrile neutropenia 3% vs 5%. Two pts in each arm died within 60 days, but no toxic deaths have occurred. Among the 230 pts so far evaluated for response (14 too early), responses, assessed by investigators, were (arm A vs arm B): complete 5% vs 8%, partial 35% vs 57%, stable 32% vs 20% progression 25% vs 12%, not evaluable 3% vs 3%. The response rate (complete+partial) was significantly higher in the FOLFOXIRI arm (65% vs 40%, $p = 0.0002$). At a median follow-up of 13.4 months 186 pts have progressed and median PFS is significantly longer in the FOLFOXIRI arm (9.8 vs 6.9 months, $p < 0.0001$) with an hazard ratio of 0.57 in favor of FOLFOXIRI.
Conclusions: This FOLFOXIRI regimen is feasible with manageable toxicities and significantly increases response rate and PFS compared to FOLFIRI. Externally reviewed response rate and updated activity and efficacy results will be presented. (Partially supported by Fondazione ARCO).

600 ORAL

Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (ACC), an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) Phase III study

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Background: Survival results in previous studies of mono- versus combination chemotherapy in ACC may have been biased by an imbalance in salvage treatments. This is the first study that prospectively evaluates sequential versus combination chemotherapy with a fluoropyrimidine, irinotecan, and oxaliplatin, and which incorporates capecitabine as fluoropyrimidine.
Patients: Patients were randomised between 1st line capecitabine, 2nd line irinotecan, and 3rd line capecitabine+oxaliplatin (arm A) vs. 1st line capecitabine+irinotecan, and 2nd line capecitabine+oxaliplatin (arm B). Primary endpoint is overall survival. Between Jan. 2003 and Dec. 2004 a total of 820 patients (pts) were randomised.
Results: The first 400 pts included in the study were considered in this analysis. On-study forms were available from 366 pts, and 350 pts were known to have entered the 1st-line treatment period. Median number of cycles (range) in arm A was 1st line 7.0 (1–30), 2nd line 6.0 (1–24), 3rdline 3.5 (1–30), in arm B 1st line 6.0 (1–26), 2nd line 3.0 (1–24). In 1st line, the most importantgrade 3–4 toxicities in arm A versus B were: hand–foot syndrome (11% vs. 2%), diarrhea (11% vs. 23%), nausea (3% vs. 9%), vomiting (3% vs 7%), febrile neutropenia (<1% vs 5%), and all grades cholinergic syndrome (0% vs 20%). In 2nd line: diarrhea (15% vs 10%), febrile neutropenia (6% vs 2%), sensory neuropathy (1% vs 7%), and all grades hypersensitivity reactions (1% vs 11%) and cholinergic syndrome (31% vs 4%). When grade 3–4 toxicity over all lines was considered, the largest differences were observed for the incidence of hand foot syndrome (12% vs 4%) and diarrhea (19% vs 25%). Incidence of thrombo-embolic events (4% vs 5%) and cardiotoxicity (1% vs 0%) was low. Sixty-day all-cause mortality was 5% (19 pts), 3% (6 pts) in arm A and 6.5% (13 pts) in arm B. Cause of death was disease progression (7 pts), sudden death of unknown cause (4 pts, all in arm B), neutropenic sepsis (3 pts), diarrhea, respiratory failure of unknown cause, pulmonary embolism, ruptured abdominal aneurysma, and bowel perforation/bleeding during NSAID use (1 pt each). Overall, 8 pts died by causes which were clearly related to treatment: 6 pts (3%) in arm A (neutropenic sepsis 4, diarrhea 2) and 2 pts (1%) in arm B (neutropenic sepsis 2). In 3/8 pts protocol violations were likely to have contributed significantly.
Conclusions: Toxicity in both arms was acceptable. Sequential treatment had a higher incidence of hand–foot syndrome, and a lower incidence of diarrhea. Many patients are still on treatment, and data are therefore subject to change. Based on these preliminary safety results, combination treatment does not appear to be more toxic to sequential treatment, but the sudden deaths during treatment with capecitabine+irinotecan need further attention.

601 ORAL

Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus Capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal carcinoma (MCRC): results of the safety and efficacy analysis

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Background: In a previous phase III study the FUFOX regimen has shown superior response rates to bolus 5-FU/FA (Mayo Clinic protocol) in patients with MCRC. The combination of capecitabine (CAP) and oxaliplatin (OX) has demonstrated good efficacy and safety results in recent phase II studies. In August 2002 we initiated a phase III trial to compare FUFOX and CAPOX as first line therapy in patients with MCRC. Here, we present the results of the safety and efficacy analysis.
Patients and methods: From August 2002 to August 2004, 474 patients (m:f = 62% vs 38%; median age 65 (range 32–86)) have been randomized to receive either FUFOX (234 pts. arm A: 5-fluorouracil 2000 mg/m^2 24 h infusion, folinic acid 500 mg/m^2, oxaliplatin 50 mg/m^2 d1, 8, 15, 22; q5 wks) or CAPOX (242 pts arm B: capecitabine 1000 mg/m^2 bid d1–14, oxaliplatin 70 mg/m^2 d1 and 8; q3 wks). All patients had measurable metastatic disease, ECOG performance status 0–2, normal renal and hepatic function.
Results: To date 2123 treatment cycles (1026 FUFOX, 1515 CAPOX) are evaluable for toxicity (median number of cycles per patient: arm A: 4, range 1–10; arm B: 6, range 1–21, table 1). Based on 233 events currently observed, median time to tumor progression (primary study endpoint) was 8 months in the FUFOX arm and 7 months in the CAPOX arm, respectively: p = NS.
Secondary efficacy parameters are detailed in table 1.

Table 1

Response Rates (ITT), %	CAPOX	FUFOX
CR	2	5
PR	45	44
SD	32	23

Table 1: Response rates.

Conclusions: These data show for the first time that both FUFOX and CAPOX have comparable efficacy profiles and response rates. As showed in previous analysis the safety profiles of both regimens are equivalent. Updated toxicity and efficacy results will be reported at the meeting.

602 ORAL

Preliminary safety of bevacizumab with first-line FOLFOX, CAPOX, FOLFIRI and Capecitabine for mCRC – First BEATrial

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Background: In a phase III pivotal trial in patients (pts) with metastatic colorectal cancer (mCRC), bevacizumab (BEV, Avastin®) increased overall survival by 30% when added to first-line IFL chemotherapy (CT). Safety data from controlled BEV trials have been described, and indicate that certain serious adverse events (SAE), primarily gastrointestinal (GI) perforations and arterial thromboembolic events (TE) occurred more often in pts who received CT with BEV than those who received CT alone.