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.

First BEAT was opened to evaluate safety events of BEV in a broader pt population using a variety of CT regimens.
Methods and material: First BEAT started in June 2004 and aims to enrol up to 2000 mCRC pts globally. Eligible pts starting with first-line CT (choice of CT is at the physician's discretion) are treated until progression with BEV (5 mg/kg every 2 weeks [5FU based CT] or 7.5 mg/kg every 3 weeks [capecitabine based CT]). SAEs include deaths, new and prolonged hospitalizations, life-threatening as well as medically significant events. BEV-related (investigators' assessment) SAE's and survival are reported as information becomes available (24 hours).
Results: By May 17, 2005, 951 pts had been enrolled in 32 countries. 606/951 pts (male 58%; median age 60 years [31% were >65 years]; PS 0–1 99%) had data for baseline analyses. Median follow-up was 4.1 months (mean 4.4); 522 pts had been followed-up for >60 days. The most common first-line CT regimens used with BEV were FOLFOX (27%), CAPOX (20%), FOLFIRI (18%) and capecitabine (7%).
Among the 942 pts that had started treatment with BEV, 257 SAEs were reported in 161 pts including 31 deaths. 60-day mortality was 2.1%. 67 BEV related SAEs, including 8 deaths ($1^{\dagger}$), were reported in 57 (6%) pts. The related SAE included 13 venous TE, 7 ($2^{\dagger}$) pulmonary embolism, 6 ($1^{\dagger}$) GI perforation, 6 ($1^{\dagger}$) bleeding, 6 diarrhea, 5 abdominal pain, 5 arterial TE, 3 fever, 2 hypertension, 1 GI inflammation, 1 peptic oesophagitis, 1 ($1^{\dagger}$) mucositis with peritonitis/sepsis, 1 ($1^{\dagger}$) ileus, 1 ($1^{\dagger}$) sudden death, 1 ($1^{\dagger}$) cardiac arrest, 1 abscess, 1 cardiac palpitation, 1 dyspnea, 1 allergic reaction, 1 surgery and 1 rigors.
Conclusions: In this ongoing, large community-based study, the safety profile of BEV in first line mCRC pts receiving a variety of CT regimens, namely FOLFOX, CAPOX, FOLFIRI and capecitabine, appears consistent with that observed in the pivotal trial. Updated safety data (including additional SAEs) will be presented.

Oral presentations (Tue, 1 Nov, 9.15–11.15)
GI – rectal cancer

603 ORAL

The Swedish rectal cancer trial – long-term effects of preoperative radiotherapy

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Background: To evaluate the long-term outcome after curative rectal cancer surgery in a material randomised to preoperative radiotherapy and surgery or surgery alone.
Patients and Methods: Between 1987 and 1990 eleven hundred and sixty eight patients were randomised in the Swedish Rectal Cancer Trial. Of these, 908 had an R0 resection, 454 of which had surgery alone and 454 had preoperative radiotherapy with 25 Gray in 5 days the week before surgery. Long-term follow-up was made by matching the curatively treated patients to three nation-wide health registries; the Swedish Cancer Register, the Hospital Discharge Register and the Cause of Death Register. Actuarial methods were used to calculate cumulative survival and cumulative recurrence rates. Groups were compared using the log-rank test and proportions with the Chi-square test.
Results: Median follow-up time was 13 years (range 3–15). The over all survival rate in the irradiated group was 38% and 30% ($p = 0.008$) in the surgery alone group. The corresponding figures for cancer specific survival were 72% *vs.* 62% ($p = 0.03$). The over all local recurrence rate in the irradiated group was 9%, compared to 26% ($p < 0.001$) in the surgery alone group. The reduction in local recurrence rates was significant in all stages (I-III) and in tumor heights up to 10 centimetres.
Conclusions: The benefits of short-term preoperative radiotherapy in terms of increased over all and cancer specific survival, as well as a reduction of local recurrences after curative rectal cancer surgery, remain after a very long follow-up.

604 ORAL

Long-term results of a randomised trial comparing preoperative short-course radiotherapy vs. preoperative conventionally fractionated chemoradiation for rectal cancer

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Background: The primary aim of the trial was to detect whether larger tumor shrinkage after chemoradiation compared to short-course radiotherapy will result in an increased rate of anterior resections. No benefit of chemoradiation was found in terms of sphincter preservation (Radiother Oncol 1994; 72:15). The current report presents a comparison of long-term results.
Material and methods: Three hundred and sixteen patients with cT3–4 resectable rectal cancer without sphincters' infiltration and with a lesion accessible to digital rectal examination were randomized to receive either preoperative short-course irradiation (5×5 Gy) with subsequent total mesorectal excision (TME) performed within 7 days or chemoradiation (50.4 Gy, 1.8 Gy per fraction plus bolus of 5-fluorouracil and leucovorin) followed by TME after 4–6 weeks.
Results: By the late-breaking abstract deadline of 15 September following data will be submitted: overall survival, disease free survival, cumulative frequency of local recurrences and late complications rate.

605 ORAL

Prognostic value of [18F] FDG PET patients treated with neo-adjuvant radio-chemotherapy for rectal cancer: long term results

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Objective: The purpose of the present study was to assess the prognostic value of [^{18}F] FDG PET performed at restaging in patients with locally advanced rectal cancer submitted to neo-adjuvant radio-chemotherapy (RCT).
Material and methods: Eighty-eight consecutive patients with histologically proven rectal adenocarcinoma, clinical stage II-III accordingly to TNM classification, were enrolled. All patients received the same neo-adjuvant RCT schedule. One month after RCT completion, all patients were restaged by ultrasound, CT scan, MRI, endoscopy and [^{18}F] FDG PET). Surgery was performed in all cases within 8–9 weeks from completion of RCT. Median follow-up after surgery was 38 months (range 6–66).
Results: In the long-term follow-up patients' group, the 5-year overall survival and disease-free survival were 83% and 73%, respectively. Multivariate statistical analysis using Cox model showed that only two parameters at restaging were prognostic independent predictors of both overall survival and disease-free survival: pathologic stage (p-Stage) and especially [^{18}F]FDG PET. In fact, the 5-year overall survival was 91% in patients with a negative PET post-RCT versus 72% in those with positive PET ($p = 0.024$), while it was 81% versus 62% ($p = 0.003$) for the 5-year disease-free survival. In PET-negative group only 8% of patients experienced distant metastases, and no patient pelvic failure. Statistical power was further increased when combining the p-Stage with the ^{18}F-FDG PET results. In particular, the 5-year overall survival was 95% in the PET-negative/p-Stage 0-I patients versus 70% in PET-positive/p-Stage II-IV patients ($p = 0.001$), while it was 93% versus 65% for the disease-free survival ($p = 0.0003$).
Conclusion: In patients with locally advanced rectal cancer treated with neo-adjuvant RCT, the combined evaluation of p-Stage and ^{18}F-FDG PET at restaging identifies a subgroup of patients characterised by good response to RCT and more favourable prognosis. In these patients a conservative surgical approach with organ preservation, like complete local excision, might be considered.