7−74) there was no difference in colonic neoplasia between those on either active treatment or placebo (Burn et al NEJM 359:2567–2578). Long term follow-up data have been accumulated on 628 of the cohort of whom 218 have developed a total of 240 cancers or adenomata. Randomisation was not divulged.
Commencing around 5 years from initial randomisation, the incidence of new cancers in the aspirin and placebo groups began to diverge. To date there have been 6 colon cancers in the aspirin treated group and 16 in the placebo group. The respective figures for all HNPCC related cancers are 18 and 31 ($p < 0.02$) The protective effect appears to persist for at least 6 years after the episode of aspirin use and correlates with the duration of aspirin use on trial.
All those at risk of Lynch syndrome related cancer should consider long term aspirin use. Plans for a large scale randomised dose finding study of aspirin in Lynch syndrome will be presented.

6001 ORAL

International randomised phase III study of capecitabine (Cap), bevacizumab (Bev) and mitomycin C (MMC) in first line treatment of metastatic colorectal cancer (mCRC): final results of the AGITG MAX trial

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Background: The addition of bevacizumab (Bev) to oxaliplatin or irinotecan doublet chemotherapy has shown benefit in metastatic colorectal cancer (mCRC). Capecitabine (Cap) +/− MMC are alternate treatments suitable for patients (pts) who are unfit for or do not require initial oxaliplatin/irinotecan. This phase III study compared Cap with Cap Bev and Cap Bev MMC. The aim was to develop a low toxicity regimen suitable for a broad population of pts with mCRC.
Methods: Previously untreated pts with unresectable mCRC considered suitable for Cap monotherapy were randomised to arm A: Cap (Cap 1000 or 1250 mg/m^2 bd d1−14 q3w), arm B: Cap Bev (Bev 7.5 mg/kg q3w) or arm C: Cap Bev MMC (MMC 7 mg/m^2 q6w). Primary endpoint: PFS, secondary endpoints: RR, toxicity, OS, QoL. Stratification was by age, PS, centre and Cap dose. Response was assessed q6w. The study was designed to detect a median PFS increase from 5.5 m (arm A) to 8 m (arm B or C) at $p < 0.025$ with 80% power in an intention-to-treat analysis.
Results: 471 pts (15 ineligible) were randomised from July 2005-June 2007. Baseline demographics were well balanced between arms with median age 67 y (range 31−86 y). Most common grade 3/4 toxicities were HFS (16%, 26%, 28%) and diarrhoea (11%, 17%, 16%) for arms (A, B, C). However, adjusted rates per cycle were similar as arms B & C received more cycles of Cap (A8.4, B10.9, C10.7). Other toxicity rates were generally $\leqslant$10%.
The study achieved its primary endpoint with a highly significant improvement in PFS for arms B & C. Efficacy data summarised in table. RR was superior in arm C vs arm A. There was no significant difference in OS between arms. Updated data relating to 2nd and subsequent line therapy received will be presented. Quality of Life (QoL) measures and utilities were similar in all arms.
Conclusions: All treatment regimens were well tolerated in a relatively elderly patient cohort. Addition of Bev +/− MMC to Cap significantly improved PFS without either significant additional toxicity or impairment of QoL. OS was similar in all arms. Cap Bev+/-MMC is an active, low toxicity regimen that may be considered as a treatment option for pts with mCRC.

	Arm A (Cap)	Arm B (CapBev)	Arm C (CapBevMMC)	BvsA	CvsA
PFS (m)	**5.7**	**8.5**	**8.4**	**HR 0.63 p < 0.0001**	**HR 0.59 p < 0.0001**
RR (%)	30	38	46	p = 0.16	p = 0.006
OS (m)	18.9	18.9	16.4	HR 0.86 p = 0.24	HR 1.00 p = 0.97

6002 ORAL

BRAF mutation is associated with a decreased outcome in patients (pts) with advanced colorectal cancer (ACC) treated with chemotherapy and bevacizumab with or without cetuximab

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Background: The efficacy of anti-EGFR monoclonal antibodies is restricted to pts with *KRAS* wildtype tumours. In this subgroup, it has been suggested that a mutation in *BRAF* was related to a decreased outcome, but data from randomized studies are not available. We previously showed that patients with a *KRAS* mutated tumour have a decreased progression-free (PFS) and overall survival (OS) when treated with chemotherapy, bevacizumab and cetuximab (CBC) compared to both pts with a *KRAS* wildtype tumour treated with CBC and compared to pts with a *KRAS* mutated tumour treated with chemotherapy and bevacizumab without cetuximab (CB) (Tol et al., N Engl J Med 2009). We here present the outcome in relation to *BRAF* mutation status.
Materials and Methods: DNA was isolated from formalin-fixed paraffin embedded primary tumor tissue from 531 ACC pts participating to a phase III randomized trial (the CAIRO2 study of the Dutch Colorectal Cancer Group) and treated with CB or CBC. The *BRAF* V600E mutation was assessed by sequencing and the KRAS codon 12 and 13 mutation status was assessed by sequencing and a real-time PCR-based assay.
Results: Both the *BRAF* and *KRAS* mutation status were evaluable in the tumour DNA of 516 eligible pts. A *BRAF* mutation was observed in the tumour of 45 pts (8.7%), 17 in the CB and 28 in the CBC arm. A *KRAS* mutation was found in 203 tumours (39.3%). None of the tumours had both a *BRAF* and a *KRAS* mutation. Pts with a *BRAF* mutated tumour had a decreased median PFS compared to pts with a wild type tumour, irrespective of the treatment arm (5.9 vs 12.2 months; $p = 0.003$ in the CB arm, and 6.6 vs 10.4 months; $p = 0.010$ in the CBC arm, respectively). The median OS was also decreased in pts with a *BRAF* mutated compared to wild type tumour in both arms (15.0 vs 24.6 months in the CB arm; $p = 0.002$, and 15.2 vs 21.5 months in the CBC arm; $p = 0.001$). In the CBC arm 125 out of 259 pts (48.3%) had a tumour with either a *BRAF* or a *KRAS* mutation, which was associated with a decreased median PFS compared to pts with *BRAF*/*KRAS* wild type tumours (7.4 vs 11.4 months, $p < 0.0001$). In the CB arm the median PFS was not significantly different in 123 pts with *BRAF*/*KRAS* mutated compared to wild type tumours (11.3 vs 11.7 months, $p = 0.35$).
Conclusions: A *BRAF* mutation is associated with a decreased PFS and OS in ACC pts treated with chemotherapy, and bevacizumab with or without cetuximab. In contrast to a *KRAS* mutation, the association with outcome is not restricted to pts treated with cetuximab.

6003 ORAL

The correlation between Topoisomerase-I (Topo1) expression and outcome of treatment with capecitabine and irinotecan in advanced colorectal cancer (ACC) patients (pts) treated in the CAIRO study of the Dutch Colorectal Cancer Group (DCCG)

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Background: Topo1 is the molecular target of the active metabolite of irinotecan, SN38. Recently, Topo1 immunohistochemistry (IHC) was shown to be predictive for outcome of treatment with irinotecan, and possibly also of oxaliplatin (Braun et al, J Clin Oncol 2008). We assessed the predictive role of TopoI in the DCCG CAIRO study in which the sequential versus the combined use of capecitabine, irinotecan, and oxaliplatin in ACC pts was investigated (Koopman et al, Lancet 2007).
Methods: Paraffin embedded blocks of the primary tumor were collected from pts included in the CAIRO study. IHC staining and blinded scoring was performed according to the method as described by Braun et al in the FOCUS study.
Results: Five hundred forty five pts (68%) were assessable for Topo1 IHC (low, <10%; moderate, 10% to 50%; or high, >50% tumour nuclei). In pts with low and moderate/high Topo1, PFS was not improved by

the addition of irinotecan (hazard ratio [HR]: 0.74; 95% CI 0.57−0.97; interaction p = 0.710). Low and moderate/high Topo1, was not associated with an overall survival benefit with first-line combination chemotherapy (HR 0.91; 95% CI 0.69−1.2, and HR 0.83; 95% CI 0.62−1.1, respectively; interaction p = 0.65).
Conclusions: We did not observe an interaction between Topo1 expression and treatment with capecitabine plus irinotecan in respect to progression free and overall survival. Using the same methodology, we could not confirm the results of Braun et al. This underscores the complexity of this molecular marker and currently prevents the use of Topo1 expression in daily practice.

6004 ORAL

Late toxicity after preoperative (chemo)radiotherapy in non-resectable rectal cancer – results from a randomized phase III study

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Background: Several studies have shown the superiority of preoperative chemoradiotherapy (CRT) versus radiotherapy (RT) alone in locally advanced rectal cancer, but the gains in overall survival are limited. Follow-up of health-related quality of life and late toxicity has therefore become very important. The aim of this study was to compare the two groups, CRT versus RT, with focus on bowel function, urinary complications and sexual function in a long-term follow-up.
Material and Methods: 207 patients with nonresectable rectal cancer were randomized to receive preoperative CRT or RT (2×25 Gy $\pm$ 5FU/leucovorin) before surgery. Extended surgery was often required. Patients in the CRT group were also given adjuvant chemotherapy for 4 months. After a minimum of 4 years (range 4−12) posttreatment, patients alive in Norway and Sweden (n = 105) were contacted. Late toxicity was assessed using validated questionnaires and a telephone interview. Bowel and urinary function were scored with the LENT SOMA scale and the St. Marks score for fecal incontinence.
Results: Of the 105 patients contacted, 78 (74%) answered questionnaires and an interview. There were no statistically significant differences between responders and non-responders. A larger proportion of patients in the CRT group had stoma (73% versus 53%, p = 0.07). A majority of patients in both groups without a stoma (12/44 in the CRT and 16/34 in the RT group) had incontinence for liquid stools and gas. 28% (12/44) of patients in the CRT group suffered from bowel obstruction, half of them needed surgery. In the RT group the comparative figures were 15% (5/34) and 12% (4/34), respectively. In both groups a majority reported no urinary incontinence (73% versus 65%), and importantly, almost all patients in both groups (95% versus 82%) reported that urinary complications had no impact on their social life. More than two-thirds of both males (44/69) and females (27/37) reported on their sexual function. Many males had severe erectile dysfunction, median IIEF scores were 4 (1−29) in the CRT and 5 (1−29) in the RT group. Only 7 and 4 women in the CRT and RT groups, respectively, reported to be sexually active the previous month. However, the majority did not worry about their sex life/lack of sex life, 9/14 and 10/13 in CRT and RT groups, respectively.
Conclusion: There were no statistically significant differences in late toxicity between the CRT and RT groups. Fecal incontinence and erectile dysfunction were frequent in both groups.

6005 ORAL

PIK3CA, BRAF and KRAS mutations and outcome prediction in chemorefractory metastatic colorectal cancer (mCRC) patients treated with EGFR targeting monoclonal antibodies (MoAbs): results of a European Consortium

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Background: Deregulations of the EGFR signaling pathway, including *KRAS*, *BRAF* and *PIK3CA* mutations can impair clinical response to EGFR targeting MoAbs in mCRC. The predictive role of *KRAS* is well validated, however the precise impact of *BRAF* and *PIK3CA* and the combinations needs to be determined. A European Consortium was set up in order to have a large sample set with sufficient power to perform this subgroup analysis.
Methods: Over 1000 formalin-fixed, paraffin-embedded samples of chemorefractory mCRC treated with EGFR targeting MoAbs were collected together with the clinical data. All samples were centrally analyzed by the Sequenom MALDI-TOF MassArray system for the following mutations: *KRAS* p.G12S, p.G12R, p.G12C, p.G12D, p.G12A, p.G12V, p.G13D, p.A146T, p.G13A, p.G13V, p.G13G, p.G13G, p.A59T, p.Q61K, p.Q61E, p.Q61P, p.Q61R, p.Q61L, p.Q61H and p.Q61H; *BRAF* p.V600E, p.V600M, p.K601E and p.D594G; *PIK3CA* p.N345K, p.R38H, p.C420R, p.P539R, p.E542K, p.E542Q, p.E545K, p.E545G, p.E545Q, p.Q546K, p.Q546E, p.E81K, p.R88Q, p.C901F, p.M1004I, p.G1007R, p.H1047Y, p.H1047R, p.H1047L, p.G1049R, p.G1049S, p.G106V, p.R108H, p.G12D, p.G118D, p.P134S, p.S158L, p.H160N, p.H701P, p.K184E and p.K179T. We correlated the mutation status with objective response, progression-free and overall survival. Furthermore we studied the associations between the mutations and their frequency.
Results: An interim analysis on 705 patients was performed looking at mutation frequency and associations between mutations. *KRAS* mutations were found in 38%, *BRAF* in 4% and *PIK3CA* in 12.2% of patients. 40/244 (16%) *KRAS* mutants and 40/402 (10%) *KRAS* wild-types had a *PIK3CA* mutation (p = 0.016 Pearson's chi-square). 1/27 (3.7%) *BRAF* mutants and 78/631 (12%) *BRAF* wild-types had a *PIK3CA* mutation (p = 0.235 Fisher's exact test). *BRAF* and *KRAS* mutations were mutually exclusive. The mutation analysis will be completed on all patients. Not all samples were analyzed at the time of abstract submission. The success rate in the first series was higher than 90%. The outcome analysis is ongoing and will be presented at the meeting for all patients.
Conclusion: This series will be the largest one presented that will define the role of EGFR pathway deregulations in patients with mCRC treated with EGFR MoAbs in the chemorefractory setting.

6006 ORAL

PIK3CA mutations predict local recurrences in rectal cancer patients

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Background: Identifying rectal cancer patients who are at risk for local recurrence would allow for refinement in selection of patients who would benefit from preoperative radiotherapy. PIK3CA, KRAS and BRAF mutations are commonly found in colon cancers, but their prevalence has not been clearly assessed in rectal cancer. In this study, we aimed to determine the mutation frequencies of PIK3CA, KRAS and BRAF and to investigate whether a mutation may be used as parameter for predicting local recurrences in rectal cancer patients.
Material and Methods: Non-irradiated tumor samples from 240 stage I-III rectal cancer patients were available from the Dutch Total Mesorectal Excision (TME) trial, in which rectal cancer patients were randomized for treatment with standardized surgery and preoperative radiotherapy or surgery only (median follow-up surviving patients 7.2 years). The sequences of exons 9 and 20 of PIK3CA, exon 1 of KRAS and exon 15 of BRAF were evaluated by PCR and sequencing using DNA extracted from freshly frozen tumor tissue.
Results: PIK3CA, KRAS and BRAF V600E mutations were identified in 19 (7.9%), 81 (33.9%) and 5 (2.1%) rectal cancers, respectively. Mutations in KRAS and BRAF were mutually exclusive (P = 0.17), which is consistent with previous studies. Although 10 tumors showed both PIK3CA and KRAS mutations, this association was not statistically significant (P = 0.07). Interestingly, PIK3CA mutations revealed a strong association with increased local recurrences (5-year risks, 27.8% vs 9.4%; P = 0.006) and the significance was unaffected when patients who received postsurgery radiotherapy were excluded (5-year risks, 26.7% vs 6.4%; P = 0.002). In univariate analysis, a PIK3CA mutation was predictive of local recurrence (hazard ratio (HR) 3.48; 95%CI 1.3−9.34; P = 0.01). In multivariate analysis, PIK3CA mutations remained as an independent predictor for the development of local recurrences (HR 3.38; 95%CI 1.24−9.18; P = 0.02), next to tumor-node-metastasis (TNM) stage.
Conclusion: PIK3CA mutations can be used as a biomarker to identify rectal cancer patients with an increased risk for local recurrences. Comparison with patients within the TME trial who did receive preoperative radiotherapy should reveal whether these patients indeed benefit from preoperative radiotherapy. Currently, our findings suggest that prospective evaluation of PIK3CA mutation status would reduce overtreatment by preoperative radiotherapy for the low risk patients who would only experience the side-effects.