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