therapy using gene *E in vitro* using MCF-7 breast cancer cells forming MTS. In order to determine the effect of the combined therapy (gene therapy and citotoxics) transfected MCF-7 MTS were treated with gradient concentrations of the drug diluted in the culture medium: paclitaxel, docetaxel and doxorubicin. We studied the action mechanism of the combined therapy: study of apoptosis and cellular cycle, and the modulation of the volumes of the MTS of tumour cells.
Results: Our results showed that the use of doxorrubicin in MCF-7 breast cancer MTS transfected with *E* gene enhanced the chemotherapeutic effect of this drug. This inhibition was greater than that obtained using the gene therapy or chemotherapy alone.
Conclusions: The transfection of gene *E* in MCF-7 MTS is able to increase the chemotherapeutic effect of drugs and specially is able to enhance the anticancer effect of the doxorubicin in comparison to the growth inhibition obtained using the gene therapy or chemotherapy alone. These results indicate that this combined therapy may be of potential therapeutic value in breast cancer.

5201 POSTER

Guidelines in breast cancer – are they keeping up with the times?

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Background: This study aimed to determine how quickly various pivotal clinical trial data in adjuvant treatment for breast cancer were adopted into local and international guidelines.
Materials and Methods: PubMed and conference Web sites were searched to identify representative trials of 3 key adjuvant advances in breast cancer: taxanes, trastuzumab, and aromatase inhibitors (AIs). The inclusion of these treatments in the following international guidelines was analyzed: American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and St. Gallen consensus. Several regional guidelines were also reviewed: National Institute for Health and Clinical Excellence (NICE; UK), Danish Breast Cancer Cooperative Group (DBCG), and German Gynecological Oncology Working Group (AGO).
Results: Early studies on taxanes as adjuvant therapy were presented in 1998 and 2000, but adjuvant taxanes were not readily adopted into guidelines. In contrast, guidelines were quickly updated (1−2 y) to recommend adjuvant trastuzumab after data were presented in 2005. Following initial data on adjuvant AIs with the release of the ATAC findings, NCCN guidelines were updated within months. The ASCO technology assessment, St. Gallen consensus, and NICE guidelines were updated several years later, but upfront AIs were not recommended over tamoxifen. With the release of data indicating an emerging survival benefit with upfront letrozole for 5 years, guidelines are being revisited, and further updates are expected. In the 2009 St. Gallen consensus vote, the majority (70%) favored upfront use of AIs.

Treatment	Representative data		Adoption into guidelines	
	Trial	Date	Guideline	Date
Taxanes	CALGB 9344	1998	NCCN	2003
	NSABP B-28	2000	St. Gallen	2007
			NICE	2006 (paclitaxel not recommended)
Trastuzumab	HERA	May 2005	NCCN	2006
			St. Gallen	2006
			NICE	2006
			ASCO	2007
AIs	ATAC	Dec 2001	NCCN	Jan 2002
			ASCO	2005
			St. Gallen	2005
			NICE	2006
AIs	BIG 1−98	Dec 2008	St. Gallen	2009
			DBCG	2009
			AGO	2009

Conclusions: Of the 3 classes of adjuvant therapy investigated in this study, the inclusion of adjuvant trastuzumab into guidelines has generally been the most rapid, and the inclusion of adjuvant taxanes into guidelines has been the slowest. Clinicians have traditionally relied on guidelines to assist them in treatment decision-making. In the current era of rapid advances in oncology, the guideline process needs to be modified to help integrate emerging evidence in a timely manner.

5202 POSTER

Deletions of PTEN and FBXW7 in breast carcinomas investigated with array comparative hybridization (aCGH) are associated with reduced survival in a long term follow up clinical cohort

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The protein mTOR (mammalian target of rapamycin) is a promising target of cancer therapy in human disease. mTOR is a key player in the PI3K-Akt pathway and the group of rapamyoid chemotherapeutic drugs seem to inhibit mTOR in a specific manner. In previous studies the *PTEN* (phosphatase and tensin homolog) and *FBXW7* (F-box and repeat domain containing 7) both seem to inhibit the mTOR level. Deletions in these tumor suppressor genes may thus be a marker for the response of rapamycin. There is evidence for a reciprocal relationship between deletions of these genes. The aim of this study was to investigate the frequency of deletions in PTEN and FBXW7 in a clinical cohort with long term follow up with a high resolution array comparative genomic hybridization platform (aCGH). Tumor tissues from a series of 212 primary breast cancer cases were sequentially collected at Ullevål University Hospital between 1990 and 94. Tissues were sampled at the time of primary surgery and snap frozen. We performed aCGH on 167 of these tumors. DNA was isolated using chloroform/phenol extraction, followed by ethanol precipitation. The aCGH-platform was the Agilent Human-Genome-CGH Microarray 244k. For detection of aberrations, we used an algorithm for segmentation of aCGH data called piecewise constant fit (PCF). The platform contained 10 oligonucleotide probes inside the PTEN gene and 26 probes withinin the FBXW7 gene, 4 in isoform 2, 7 in isoform 3 and 26 for isoform 1. Gene deletion was defined as a value of less than −0.3 of the segmented data on a log2-scale. Statistical analyses of clinical data and survival analyses were performed using SPSS 16.0.
Many significant genetic alterations were found, with a large heterogeneity between the different tumors. In our cohort we found 29 deletions of PTEN (17.4%) and 29 deletions of FBXW7 (17.4%). 12 of these samples (5.7%) harboured a combined loss of these tumor suppressor genes. The survival for patients with a loss in the FBXW7 gene had a significantly reduced survival compared with no loss with a p-value of 0.007. For a PTEN loss the same significant difference were seen ($p < 0.005$). The subset of samples with a combined loss shows evidence of reduced survival compared to loss of one gene and suggests an additive effect of this combinated deletions. The detailed aCGH profiles and clinical data will be presented.

Gastro-intestinal malignancies − Colorectal cancer

Oral presentations (Mon, 21 Sep, 11:00−12:45)

Gastro-intestinal malignancies − Colorectal cancer I

6000 ORAL

Aspirin prevents cancer in Lynch syndrome

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CAPP2 recruited 1009 eligible carriers of Lynch syndrome (HNPCC) to a randomised controlled trial of 600 mg aspirin and/or 30 g Novelose (resistant starch) in 43 centres worldwide. After a mean of 29 months (range

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

N. Tebbutt[1], V. Gebski[2], K. Wilson[3], M. Cummins[3], B. Robinson[4], A. Broad[5], D. Cunningham[6], J. Simes[3], M. Stockler[3], T. Price[7]. *[1]Austin Health, Medical Oncology, Melbourne, Australia; [2]NHMRC Clinical Trials Centre, Statistics, Sydney, Australia; [3]NHMRC Clinical Trials Centre, Oncology, Sydney, Australia; [4]Christchurch Hospital, Medical Oncology, Christchurch, New Zealand; [5]Geelong Hospital, Medical Oncology, Geelong, Australia; [6]Royal Marsden Hospital, Medical Oncology, London, United Kingdom; [7]Queen Elizabeth Hospital, Medical Oncology, Adelaide, Australia*

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