percentage for nausea (p= 0,0005) and vomiting (p= 0,0083). No significant differences were observed for specific sensory and motoric neurotoxic symptoms, except for a better skilfulness in the AM group (p=0,0404). In conclusion, AM improved sensory neuropathy according to NCI-CTC and results from objective neurological assessment, but there were almost no differences in self-estimated specific sensory or motoric symptoms. Disadvantages with regard to other toxicities and inconsistent results for QoL demand further evaluation of neuroprotection with AM in the treatment of OC. At this moment the presented results do not justify a standardized additional application of AM to platinum/taxane-based chemotherapy.

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## Topotecan versus treosulfan in recurrent ovarian cancer after initial chemotherapy with platinum and paclitaxel. a prospective randomised phase III study of the AGO ovarian cancer study group.

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**Background:** After initial radical debulking surgery followed by combination chemotherapy most ovarian cancer patients will eventually relapse and will be in need of further treatment. Standard chemotherapy for recurrent disease after first line treatment with carboplatin and paclitaxel is not yet defined. Therefore, this multi-centre, prospective randomised trial, was conducted to compare the topoisomerase I inhibitor topotecan with the alkylating agent treosulfan in patients with relapsed ovarian cancer.

**Material and Methods:** The study was undertaken to define the progression-free survival time and the response rate. Patients were stratified according to treatment free interval: relapse between 0-6 or 6-12 months after end of primary treatment (2nd line) or relapse after re-induction chemotherapy with a platinum-containing regimen (3rd line). The therapy consisted of 1.5 or 1.25 (3rd line) mg/m* topotecan, d1-5 every three weeks or 7.0 or 5.0 (3rd line) g/m* treosulfan. In patients with SD or PR, treatment was continued until disease progression or intolerable toxicity occurred.

**Results:** 357 patients were recruited (topotecan 178, treosulfan 179), 8 patients were withdrawn after randomisation. Patient characteristics were equally distributed between the two groups. Significantly more patients progressed after treosulfan treatment compared to topotecan treatment (62.5% vs. 28.4%, respectively). Response data were validated by external radiological review. Haematologic toxicity grade 3/4 was more frequently observed during topotecan therapy: neutropenia in 46.8% vs. 5.4%, thrombocytopenia in 7.4% vs 1.5% and anaemia in 4.3% vs. 1.0% of the courses compared to treosulfan. Grade 3/4 infection was 2.9% and 1.1% for topotecan and treosulfan, respectively, demonstrating no significant clinical consequences caused by topotecan haematologic toxicity. Non-haematologic toxicities were mild and apart from alopecia, comparable in both treatment groups. The progression-free survival was 5.4 months in the topotecan group and 3.0 months in patients treated with treosulfan ($p < 0.0001$, all patients). The analysis of the subgroups is still ongoing.

**Conclusion:** This clearly stratified randomised study in exactly defined recurrent ovarian cancer patients after carboplatin/paclitaxel initial therapy demonstrates that, both regimens are well tolerated without clinically relevant side effects. It can therefore be concluded that, topotecan may be defined as the new standard in early recurrent ovarian cancer because of the improved progression free survival and remission rate.

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## Prognostic significance of P53, EGFR and Her-2 expression in borderline and epithelial ovarian cancer.

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The study was approved by the Danish Ovarian Cancer Study Group (DACOVA), Odense University Hospital.

**Background:** Epithelial ovarian cancer (EOC) continues to represent a challenge in cancer treatment despite advances especially in the application of new cytostatic drugs. Several aspects are not yet elucidated and important prognostic factors still need to be defined.

Several molecular-biological factors have been investigated in order to reveal new prognostic factors. Prior studies have assessed the prognostic relevance of P53-protein, EGFR and Her-2 receptors using immunohistochemical methods. So far no previous study has evaluated the prognostic significance of all three factors including a large number of patients with a long follow-up period. The objective of the present study was to evaluate the prognostic significance of p53, EGFR and Her-2 in relation to currently known prognostic factors.

**Material and methods:** The study was based on two cohorts diagnosed from 1981-86 and 1991-94. 1073 patients were retrieved from the registry of DACOVA. Archival paraffin-embedded tissue blocks from the primary surgery were retrieved from the regional departments of pathology. One senior gynaecological pathologist who had no knowledge of clinical data and outcome performed histo-pathological revision. Only patients with confirmed borderline or frank epithelial ovarian cancer at revision were included. Representative samples of tissue were chosen from each patient and three tissue-slides were stained immuno-histochemically to assess p53, EGFR and Her-2.

The slides were evaluated semi-quantitatively in a light-microscope by one of the investigators who had no knowledge of clinical data and outcome. One hundred slides from each factor were selected by random in order to evaluate inter and intra-observer variation.

**Results:** From the initial 1073 patients 202 were excluded at time of revision. Another 3 patients were excluded just prior to statistical analysis due to missing data on revision, resulting in subset off 868 patients. Preliminary results including univariate analyses show a statistically significant association between overexpression of p53 ($p<0.001$) and Her-2 (p 0.027) and decreased survival. EGFR-overexpression was not significantly associated with a decrease in survival (p 0.15). The classical prognostic factors age, stage, histology and grade were all significantly associated with survival. Multivariate analyses are in preparation and will be presented at the conference.

Reproducibility for all receptors was acceptable with kappa-values between 0.57 0.88.

**Conclusions:** Preliminary results indicate that p53 and Her-2 may be defined as prognostic factors in epithelial ovarian cancer; EGFR, however, did not prove to be a prognostic factor.

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## HER2- expression in advanced ovarian cancer: A prognostic and predictive marker? An Study of the AGO Ovarian Study Group

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In contrast to breast cancer the role of HER2 overexpression in ovarian cancer is under discussion. Up to now only small studies with contradictory results are published. The aim of this study was to analyse the role of HER2 overexpression in a uniform treated population of patients with advanced ovarian cancer, as a prognostic and/or predictive factor.

**Materials and methods:** The paraffin blocks of 361 patients from the AGO Ovar-3 trial were retrospectively analysed for HER2 expression (immunhistochemical DAKO antibody, and with FISH). The HER2 data were correlated for clinical factors.

**Results:** An expression of HER2 was detected in 25% of the tumours. Immunhistochemical Scores of e2 were observed in 9% (7% Score 2, 2% Score 3) of the tumours. The results of immunhistochemical analysis and the FISH method were identical. Statistical analyses show that these 361 patients are representative for the whole group of 798 patients from the Ovar-3 trial. No correlation could be observed for the classical clinical factors, or for response rate. Also no different (HER2 overexpression vs no overexpression) in disease-free, as well for overall survival was observed.

**Conclusion:** HER2 overexpression in advanced ovarian cancer is rare. No prognostic or predictive importance could be shown.

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## Phase I study for treatment of ovarian cancer patients with symptomatic ascites using the trifunctional bispecific antibody removab® (anti-CD3 X anti-EpCAM).

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**Background:** A new class of trifunctional bispecific antibodies has been developed for targeted therapy of epithelial tumors. Due to binding sites specific for tumor cells (EpCAM), T lymphocytes (CD3) and accessory cells (FcgRI/III) the antibody induces tumor specific cell mediated cytotoxicity in the peritoneal cavity.

**Patients and methods:** In the currently ongoing phase I study removab® was administered 4 times over 10 days in escalating doses by 6h intraperitoneal infusions, respectively. Pts had undergone 4 prior chemotherapies in median.

**Results:** To date, preliminary results of the first 16 pts are available. Patients were treated with total doses of 35 μg (3 pts), 60μg (2 pts), 80μg (1 pt), 130 μg (3 pts), 160 (1 pt), 180 μg (3 pts) and 280 μg (3 pts). So far, no dose limiting toxicity has been observed. Drug related adverse events (ADR) noted in more than 1 patient were fever (n=12), abdominal pain (n=11), vomiting (n=8), nausea (n=6), fatigue (n=4), exanthema (n=2), hypotension (n=3), hypertension (n=2), abdominal cramps (n=2). All ADR seen were mild to moderate (grade 1 to 2), except fever with grade (gr) 3 in 1 pt and hypertension with gr 3 in 1 pt. The following laboratory abnormalities (> gr 1) have been observed: elevation of liver enzymes (n=4; 2 gr 3), alkaline phosphatase (n=5; 2 gr 3) and bilirubine (n=3; 2 gr 3). Almost all patients showed a transient, clinically non-significant lymphocytopenia. Leukocytosis was also common. All pts responded to therapy. Immunocytochemical examination of ascites fluid showed a reduction of tumor cells by 4 logs at least, in most cases by more than 5 logs. In 5/16 pts no tumor cells were detectable after therapy. The disappearance of tumor cells correlated significantly with a reduced ascites production. Remarkably, only 1/16 pts required further paracentesis within 28 days after last dose (end of study).

**Conclusion:** Our preliminary results show a good tolerability of removab® in general without major toxicities and significant treatment effects on malignant ascites in ovarian cancer. Thus, the new concept of trifunctional antibodies offers promising perspectives in tumor therapy.

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## Serendipitous findings of occult fallopian tube carcinoma in BRCA 1/2 germ line mutation carriers at prophylactic surgery

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**Background:** Carriers of a BRCA-1 or 2 mutation are at increased risk of developing breast and ovarian cancer. Prophylactic surgery has proven to reduce the risk of coelomic epithelial and ovarian cancer by 96 percent. The purpose of this study is to assess the risk of occult fallopian tube or ovarian cancer at prophylactic (salpingo)- oophorectomy specimen at the Antoni van Leeuwenhoek Hospital in a series of high risk women.

**Patients and methods:** The medical files and histological slides of patients, who had undergone prophylactic surgery, were reviewed. The patients were carrier of a BRCA-1 or 2 mutation or were member of a hereditary breast / ovarian cancer (HBOC) family.They were not suspected of having any tumor before surgery, determined by patient history, pelvic examination, transvaginal examination or serum CA-125 determination.

**Results:** From January 1990 to November 2001, 141 women underwent prophylactic surgery. Forty of whom had a bilateral oophorectomy and 101 women a bilateral salpingo-oophorectomy. Ninety-four were tested positive for a BRCA-1 or 2 mutation. Five occult carcinomas were found (3,5%). Three of these five were fallopian tube carcinomas and the pathology reports of the other two showed an ovarian carcinoma. All of these five patients had a BRCA mutation. In the follow-up, three patients (2,1%) developed a peritoneal papillary serous carcinoma; 27, 33 and 72 months after oophorectomy.

**Conclusion:** HBOC patients are not only at risk for ovarian cancer but also for fallopian tube carcinoma. We recommend prophylactic salpingo-oophorectomy and not only oophorectomy in women at high risk of developing fallopian tube carcinoma or ovarian cancer.

# Gastro-intestinal tumours

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## Phase III trial comparing Epirubicin, Cisplatin and 5-FU (ECF) versus 5FU, Etoposide and Leucovorin (FELV) in previously untreated patients with advanced biliary cancer.

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FELV has demonstrated an overall response rate (ORR) of 8% and a survival benefit compared to best supportive care in advanced biliary cancer but with significant toxicity (41% grade 3/4 toxicity). ECF has demonstrated an ORR of 40% with minimal grade 3/4 toxicity in this setting. Thus this multicentre randomised phase III trial was designed to compare the safety and efficacy of ECF versus FELV in patients with previously untreated locally advanced and metastatic biliary cancer.

**Methods:** Eligible patients had WHO performance status (PS) 0-2, adequate liver, renal and hepatic function, written consent and received no prior chemotherapy or radiotherapy. Patients were randomised to treatment with stratification for centre and histology. ECF treatment consisted of Epirubicin 60 mg/m2, Cisplatin 60 mg/m2 and 5FU 200mg/m2 daily by continuous infusion every 3 weeks for a maximum of 8 cycles. FELV consisted of 5FU 600 mg/m2 IV bolus days 1-3, Etoposide 120 mg/m2 IV infusion days 1-3 and Leucovorin 60mg/m2 IV bolus days 1-3 every 3 weeks. Response assessment by CT scan according to WHO criteria took place at 12 and 24 weeks.

**Results:** 50 patients were accrued between June 1997 and January 2002. 45 and 47 are evaluable for response and toxicity. Baseline characteristics were comparable in the two treatment groups with a median age 57 (range 39-73) years, WHO PS were 0,1,2 in 10%, 72% and 18% respectively, metastatic disease in 60%, adenocarcinoma 100%. No statistically significant differences in ORR or survival parameters were observed. The ORR for FELV was 15.8% versus 19.2% for ECF. The median overall survival (OS) for FELV was 367 days [95% CI: 251- 483] and 275 days for ECF [95% CI: 189-361]. One serious adverse event resulting in death occurred on the FELV treatment arm. Grade 4 neutropenia was observed in 19% of patients treated with ECF versus 46% in the FELV arm. Grade 3 infection was reported in 17% of patients receiving ECF versus 30% in the FELV group. The incidence of other non-haematological adverse events was similar in the two groups.

**Conclusion:** ECF has demonstrated similar efficacy with significantly less acute toxicity compared to FELV in untreated advanced biliary cancer.