NSCLC. We conducted a prospective multicenter randomized phase III study with survival as primary endpoint. From June 1995 to Oct. 1997, a total of 210 patients (pts) were accrued to the trial; 104 were randomized to CC arm; CDDP 80 mg/m^2 on day 1 and CPT-11 60 mg/m^2 on days 1, 8, 15 q 4 weeks 106 to the control CV arm; CDDP 80 mg/m^2 on day 1 and VDS 3 mg/m^2 on days 1, 8, 15 q 4weeks. All pts were previously untreated, ECOG PS 0-2 and stage IV or Stage IIIB, with no symptomatic brain metastases. Both arms were well-matched with regards to sex, age, stage and PS. 199 pts were assessable for the response and toxicity. Stage IIIB: 41%, Stage IV: 59%, PS 0-1: 95%, PS 2: 5%. The objective tumor response was similar in both treatment groups, with 29% partial response (PR) in the CC pts and 22% PR in the CV. The incidence of grade 4 neutropenia was significantly higher in the CV than in the CC (18% vs 50%; P < 0.001). Conversely, the incidence of grade 3 or worse diarrhea was higher in the CC than in the CV (13% vs 1%; P < 0.001). The incidence of other toxicity was similar in the two groups. Median survival time was 45.4 weeks for CC, 49.9 weeks in CV (p = 0.786). The preliminary results suggest that the both groups are active combination in advanced NSCLC with similar response rate and survival.

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Pre-operative serum levels of angiogenic tumour markers in non-small cell lung cancer and its impact on survival

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Purpose: Angiogenesis is an important step in the progression of tumours. Several angiogenic factors have been discovered so far and two of the most studied are bFGF and VEGF. Indications are that both might have prognostic information concerning metastasis and survival. Yet, earlier studies of these angiogenic factors in sera have not been conclusive concerning prognostic information.

Patients and Methods: Our group have analysed the levels of bFGF and VEGF in preoperatively collected sera from 58 patients with a histo-pathological verified diagnosis of non-small cell lung cancer, limited disease. A semi-quantitative enzyme linked immunosorbent assay were used for detection of bFGF and VEGF. A cut-off level at the 95 percentile of a normal control subject group both for VEGF and bFGF were estimated at 500 pg/ml and 7.25 pg/ml, respectively.

Results: VEGF; Pre-operative levels of VEGF in sera were detected in all patients (median value 304 pg/ml, range 93–1554 pg/ml), 12 patients had elevated levels as defined by the cut-off level. Pre-operative levels of VEGF proved to be significantly correlated to survival, both as a continuos variable and when cut-off level were used (p-value = 0.006). In univariate analysis relapse was significantly correlated to high levels of VEGF (p-values < 0.05). bFGF; Pre-operative levels of bFGF in sera were detected in 56 patients (median value 4.60 pg/ml, range 0–43.02 pg/ml), 18 patients had elevated levels as defined by the cut-off level. When used as a continuos variable a significant correlation (p-value = 0.0028) could be demonstrated regarding survival.

Conclusion: Both bFGF and VEGF proved to have statistical significant association to survival in patients with non-small cell lung cancer.

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Genetic polymorphisms of cytochrome P4501A1 and glutathione S-transferase M1: A lung cancer case control study

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150 lung cancer patients and 300 age and sex matched control subjects have been examined for the association between polymorphisms of the CYP1A1 gene and homozygous deletion of the GSTM1 gene and lung cancer risk among Caucasians.

Methods: The CYP1A1 polymorphisms were detected by PCR/RFLP using DNA from peripheral white blood cells: the mutation m1 (MspI polymorphism in the 3'flanking region), m2 (BsrDI polymorphism in exon 7) and m4 (BsaI polymorphism is located two bp upstream from m2). GSTM1 genotype has been analyzed by PCR. Differences between groups were calculated by using Pearsons chi-square test.

Results and Conclusion: We could not find any significant difference between patients and controls for the homozygous and heterozygous MspI polymorphism. In contrast cases with heterozygous BsrDI polymorphism were at greater risk for adenocarcinoma (OR: 2.50; CL: 1.19–5.24; P < 0.01). The BsaI polymorphism was higher in control subjects than in patients and may therefore not represent a susceptibility factor for lung cancer. Our results show no influence of GSTM1 null genotype for lung cancer risk (OR: 1.04; CL: 0.69–1.57). Recruitment for this study is ongoing in order to further verify the obtained data.

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Æ-941, an inhibitor of angiogenesis: Rationale for development in combination with induction chemotherapy/radiotherapy in patients with non-small-cell lung cancer (nsclc)

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Æ-941, a standardized shark cartilage extract, shows antiangiogenic and antimetalloprotease activities in vitro and ex ovo. It was selected by the US National Cancer Institute for phase III clinical evaluation of its efficacy and safety in advanced NSCLC patients. This double-blind placebo-controlled study will evaluate the effect on survival of treatment in inoperable stage III patients. The preclinical rationale for this study is based on the antimetastatic activity of Æ-941 in the Lewis Lung Carcinoma mouse model where a 70% reduction in pulmonary metastases was observed. Æ-941 was additive to cisplatin in reducing the number of lung metastases (83% reduction in combination compared to 54% with cisplatin alone). No mortality and no loss of body weight were observed at 500 mg/kg, the highest dose administered. Toxicology studies demonstrated no dose-limiting toxicity or target organ. The clinical rationale to support this phase III trial is based on the safety profile and clinical benefit obtained in the following studies. During a phase I/II study, 80 refractory lung cancer patients (64% with distant metastases) received Æ-941 in monotherapy (5 to 95 mg/kg/day orally). Patients receiving Æ-941 at 240 ml/day showed greater clinical stability in analgesics consumption and weight loss compared to patients during the first 12 weeks. Additionally, 72 refractory prostate cancer patients received Æ-941 in monotherapy in this study. No serious adverse events were observed in these two cohorts; seven percent of non-serious adverse events were related to Æ-941, most commonly nausea, vomiting. In another study, 61 patients received Æ-941 in combination with chemotherapy and/or radiotherapy. No serious adverse events occurred with Æ-941 in this cohort. In all clinical studies involving 375 patients (194 treated >3 months), only one drug-related serious adverse event was reported (hypoglycemic episode in a type II diabetic patient with renal cell carcinoma). Based on the potential antimetastatic activity of Æ-941 demonstrated in the Lewis lung cancer model, the excellent clinical safety profile and the preliminary dose trend observed, it is proposed to evaluate the effect of Æ-941 on survival in a randomized double-blind placebo-controlled clinical study in patients with locally advanced disease receiving induction chemotherapy and radiotherapy.

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Phase II study of gemcitabine (G) and cisplatin (P) in advanced nsclc. Focus on quality of life (QoL)

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The combination of G and P has been shown to be active in advanced NSCLC but the impact of this regimen on QoL is not well established. Aim of study was to evaluate this regimen in terms of both, toxicity, activity and its effect on QoL Eighty pts with advanced NSCLC (68 men and 12 women, median age 61 years, range 40–75, median PS 80, range 60–100, 40 stage IIIB and 40 stage IV) received G (1000 mg/m^2, d. 1, 8 and 15) and P (100 mg/m^2, d. 2); q 28 d. QoL was assessed with the EORTC QLQ-30 and LC-13 questionnaires. Total number of 416 courses was administered (median 6, range 1–9). The main toxicity was myelosuppresion; grade 3/4 neutropenia, thrombocytopenia and anemia occurred in 55%, 53% and