groups, however pemetrexed appears to be more effective for non-squamous than for squamous histology. A possible explanation for this result is the previously observed overexpression of TS in squamous cell carcinoma.

	Non-squamous group		Squamous group	
	Pemetrexed (n = 205)	Docetaxel (n = 194)	Pemetrexed (n = 78)	Docetaxel (n = 94)
% ECOG PS 2	12.5	10.1	8.3	17.4
% TSPC <3 months	51.0	51.0	48.7	41.9
% Stage IV	81.5	78.9	57.7	66.0
% Male	60.5	69.1	89.7	88.3
Median OS, months	9.3	8.0	6.2	7.4
OS HR (95% CI)	0.778 (0.607, 0.997)		1.563 (1.079, 2.264)	
Median PFS, months	3.1	3.0	2.3	2.7
PFS HR (95% CI)	0.823 (0.664, 1.020)		1.403 (1.006, 1.957)	

6522 POSTER

EGFR mutations and response to TKIs therapy in NSCLC patients pre-treated with chemotherapy

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Background: The aim of this work was to study the association between EGFR mutations (mut) and response to conventional chemotherapy (CHT) and tyrosine kinase inhibitors (TKIs) in NSCLC pts of Caucasian origin.
Methods: This retrospective analysis was conducted on 103 consecutive stage I to IV NSCLC pts treated with TKIs (gefitinib or erlotinib) from July 2002 to November 2006 after failure of platinum-based CHT. Genomic DNA was isolated from paraffin-embedded tumor specimens, amplified for EGFR (exons 18 to 21) by touchdown hemi-nested PCR and sequenced in both sense and antisense directions. Response to CHT and TKIs was assessed according to RECIST criteria.
Results: Median age was 60 yrs (range 25−81.5); M/F: 59/44, ECOG-PS 0/1/2/3:68/30/4/1; stage: I/II/III/IV 4/5/35/59; adeno/bac/squamous/large-cells/other:66/9/20/3/5; never/former/current smokers: 26/20/36. EGFR mut were detected in 19 pts (18.5%); 13 (13.8%) deletions in exon 19, 3 (2.9%) point mut in exon 20 (one pt had 2 mutations) and 3 (2.9%) missense mut in exon 21. No associations were detected between EGFR mut and adeno/bac histotype ($p = 0.51$), smoke ($p = 0.23$) and gender ($p = 0.14$). Disease control rate to TKIs therapy was 54.4%, including 1 CR (pt. with EGFR mutation), 21 PR and 34 SD and objective response rate (RR) was 42%. Median time to progression was 4.4 and median survival 23.7 months. EGFR mut had a significant impact on response (PR/CR, 42% $p = 0.015$) to TKIs while they did not influence response to CHT. Cox's multivariate analysis including gender, smoke, stage and histotype showed that EGFR mut did not reach statistical significance for progression free survival (PFS) ($p = 0.52$) and overall survival (OS) ($p = 0.50$); only adeno/bac histotype was a prognostic factor for longer PFS ($p = 0.01$) and OS ($p = 0.04$).
Conclusions: In our experience EGFR mut seem to influence RR in pts treated with TKIs after platinum-based CHT. These data will be refined by FISH analysis of EGFR gene copy number, immunohistochemistry for EGFR and phosphorylated Akt (p-Akt) protein and KRAS mutations.

6523 POSTER

Clinical and potential prognostic significance of serum mesothelin and osteopontin in chemotherapy treated patients affected by malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive tumour for which no fully reliable serum tumour markers are available for diagnosis and monitoring treatment response. Candidate biomarkers for MPM diagnosis include soluble serum mesothelin-related peptides and osteopontin, and novel ELISA systems have recently been developed for their detection in the sera of MPM patients. The aim of this work was to determine whether a correlation exists between these serum markers and clinical response.
Patients and Methods: serum of 15 patients (11 males, 4 female; median age 61 years) with histologically proven, inoperable MPM were tested; samples were collected before and after at least 2 cycles of chemotherapy. Chemotherapy was always pemetrexed and a platinum compound; only one patient received second line chemotherapy with gemcitabine and vinorelbine. Responses after chemotherapy were recorded according to RECIST criteria. Evaluations were always made by two independent physicians on spiral CT scans.
Results: 8 stable diseases, 2 partial response 1 complete response and 4 progressive diseases have been observed. A strong correlation was observed among Osteopontine and Mesothelin serum levels (R sq linear 0.83 $p < 0.001$). No clear relationship resulted between clinical responses and the levels of the two markers. The patient with a partial response showed the lowest level of mesothelin before treatment, value that declined toward zero after chemotherapy, and a very low level of Osteopontine, which became again the lowest after chemotherapy. Mean level of mesothelin before treatment in responders was considerably lower than in non responders or in stable disease (1.46 vs 5.55).
Conclusions: Osteopontine and Mesothelin levels in serum of MPM are strongly correlated. Clinical response (progression and stable diseases) does not appear to be related to markers levels even if the only patient with partial response showed the lowest levels of the two markers. Other patients will be added to the study and the follow-up will prosecute to evaluate the predictive significance of these two markers and their relationship with patients' survival.

6524 POSTER

Primary tumour standardized uptake value (SUV max) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Staging Project

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Background: FDG-PET is an effective imaging technique for assessing cTNM in NSCLC. The prognostic role of SUV max, measured on the primary tumour, has been suggested in several studies of limited sample sizes. We aimed to assess more precisely its effect on survival by aggregating results of individual studies in a meta-analysis of the literature.
Methods: We searched for all studies assessing the prognostic role of SUV max on survival in NSCLC. We evaluated the methodology of each eligible study (using a non validated quantitative scale with 44 points for the clinical data and 40 points for the FDG-PET data, designed for the purpose of the review). For each publication, we extracted an estimate of the hazard ratio (HR) for comparing patients with a low or high SUV and aggregated the individual HRs into a combined HR, using a random-effects model.
Results: Eleven studies including NSCLC only, published between 1998 and 2006, were eligible. Most of them included patients with stages I to III/IV and used a SUV assessment corrected for weight. Numbers of patients ranged from 38 to 162 (total: 1108); 9 studies identified a high SUV as a poor prognostic factor for survival and 2 concluded to a non significant effect. The qualitative evaluation provided a median of 61% for the clinical data and of 50% for the FDG-PET data. SUV measurement and threshold for defining high SUV were study dependent, 7 studies looked for a "best" cut-off (maximizing the logrank test statistic) however without adjusting the p value for multiplicity.

	Number of patients	HR	95% CI
All studies (n = 11)	1108	2.13	1.54−2.95
"Best cut-off" excluded (n = 6)*	456	1.77	1.01−3.12
Stage IV excluded (n = 5)	558	2.22	1.38−3.58

*for two studies, it was possible to use median value of SUV max instead of the author's best cut-off

Conclusion: Our MA suggests that SUV max measured on primary tumour is of prognostic value for survival in NSCLC; the next step is to confirm these results in a MA based on individual patients data allowing to perform multivariate analysis taking into account well known prognostic factors.

6525 POSTER

Phase II study investigating the efficacy and safety of continuous daily sunitinib dosing in previously treated advanced non-small cell lung cancer (NSCLC)

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Background: Overexpression of the vascular endothelial growth factor receptor (VEGFR) and VEGF expression in NSCLC are associated with increased tumor angiogenesis and reduced survival in NSCLC patients (pts). Sunitinib malate (SUTENT®; SU) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3. In the first pt cohort of this study, SU on a 4/2 schedule (4 wks on, 2 wks off treatment) demonstrated a partial response (PR) rate of 11% in pts with recurrent advanced NSCLC (Socinski, ESMO 2006). In the second pt cohort of this phase II, multicenter study, a continuous dosing (CD) schedule of SU was evaluated for efficacy and safety.
Patients and Methods: Eligible pts had stage IIIB/IV NSCLC previously treated with $\leqslant$2 chemotherapy regimens, ECOG PS $\leqslant$1 and adequate organ function. Pts received SU 37.5 mg/d continuously in 4-wk cycles. The primary endpoint was RECIST-defined objective response rate. Secondary endpoints included duration of response, progression-free survival (PFS), overall survival (OS) and safety.
Results: 47 pts were treated with SU 37.5 mg/d on the CD schedule. Baseline characteristics included: median age 60 yrs (range 37–81); male 57%; ECOG PS 0/1/2 49%/49%/2%; adenocarcinoma 53%, squamous cell carcinoma 15%, other 32%. A median of 3 (range 1–12) SU cycles were initiated. SU was generally well tolerated. Frequently reported adverse events (AEs) included fatigue/asthenia, pain/myalgia, nausea/vomiting, dyspnea, diarrhea and stomatitis/mucosal inflammation, and most were Grade (Gr) 1/2 in severity. Gr $\geqslant$3 AEs included fatigue/asthenia (17%), dyspnea (9%), hypertension (6%), hypoxia (6%), and pleural effusion (6%). Treatment-related serious AEs included (n = 1, each): hypoxic respiratory failure (Gr 3), congestive heart failure (Gr 4), worsening of toxic shock syndrome (Gr 5) and abdominal pain (Gr 2). 1 pt (2%) achieved a confirmed PR. 8 pts (17%) had stable disease for >3 months, of whom 4 had SD for >6 months. Median PFS was 12.3 wks (95% CI: 8.9–16.0). Median OS has not yet been reached.
Conclusions: SU 37.5 mg/d on a CD schedule has an acceptable safety profile in previously treated NSCLC pts and is associated with promising antitumor activity. Further study of CD SU in combination with other treatments for NSCLC is warranted.

6526 POSTER

Review of pulmonary haemorrhage (PH) in non-small cell lung cancer (NSCLC) subjects receiving bevacizumab and cisplatin plus gemcitabine on protocol BO17704

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Background: Bevacizumab, (Avastin®, B), in combination with cisplatin/gemcitabine, prolongs progression-free survival (PFS) in the first-line treatment of advanced NSCLC. Pulmonary haemorrhage (PH) was reported in a phase II study of B plus chemotherapy in NSCLC, leading to the exclusion of predominantly squamous cell carcinoma in subsequent NSCLC trials.
Methods: Subjects were treated on protocol BO17704, a randomised, double-blind phase III study of cisplatin/gemcitabine (CG) +/− B (7.5 or 15 mg/kg) for up to 6 cycles followed by B until disease progression, for first-line treatment of advanced/recurrent non-squamous NSCLC. Patients with prior grade $\geqslant$2 haemoptysis, or with lesions abutting or invading major blood vessels, were excluded. PH cases were identified by reported Adverse Event (AE) MedDRA Preferred Terms (PT). The following PTs associated with PH were found in the BO17704 database: haemoptysis, respiratory tract haemorrhage, bronchial haemorrhage. In addition, a clinical review of all serious bleeding on BO17704 reported to the Roche Databases (RDB) was performed to identify possible additional cases of PH.
Results: Central lesions, exclusive of lymph nodes, were reported in 381/1043 (36.5%) of subjects overall.

Pulmonary haemorrhage grade 3–5 adverse events on BO17704 and ECOG 4599

	BO17704			E4599
	Placebo arm n = 327 n/%	7.5 mg/kg B arm n = 330 n/%	15 mg/kg B arm n = 329 n/%	15 mg/kg B arm n = 427 n/%
Grade 3–5 PH	2* (0.6)	5 (1.5)	3* (0.9)	10 (2.3)

Events in the table were as reported through the AE case report form (8 cases) or via clinical review of the RDB* (2 cases). There was 1 fatal event in the placebo arm and 1 fatal event in the 15 mg/kg B arm; 4 of 5 grade 3–5 events in the 7.5 mg/kg B arm were fatal; and all grade 3–5 events in the 15 mg/kg B arm were fatal at the time of clinical data cut-off. Of grade 3–5 PH events identified, 2 of 10 were associated with thrombocytopenia (grade 1 and 3). Grade 3–4 thrombocytopenia occurred at a rate of 23–27% across treatment arms.
Conclusions: The incidence of severe PH in BO17704 (1.2% across both B-containing arms) was lower than in E4599 (2.3%). Most PH events in BO17704 occurred in the 7.5 mg/kg B arm, although study treatment duration was slightly longer in the 7.5 mg/kg B arm (mean 4.94 cycles) than in the 15 mg/kg B arm (mean 4.63 cycles).

6527 POSTER

Intravenous administration of PLK-1 siRNA with atelocollagen as an in vivo drug delivery system (DDS) inhibits the growth of murine liver metastasis of lung cancer

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Background and Purpose: Despite advances in medical oncology, about a million have died of lung cancer worldwide. The current treatments are insufficient, making a more effective novel therapy necessary. PLK-1 is a family of polo-like kinases (PLKs) and is crucial for the regulation of cell division. It has been reported to overexpress in many cancer types, and its elevated expression is positively correlated with malignancy and a poor prognosis for the patient. We investigated in vitro effects of PLK-1