because of toxicity or tumour progression, were randomized to receive daily oral doses of ZD6474 (300 mg) or gefitinib (250 mg) until disease progression or evidence of toxicity (part A). After a washout period of 4 weeks, patients were then eligible to switch to the alternative treatment, which continued until a withdrawal criterion was met (part B). The dual primary objective was evaluation of time to progression (TTP) and assessment of safety/tolerability.
Results: In part A, 168 patients from 35 centres were randomized to receive initial treatment with ZD6474 (n = 83) or gefitinib (n = 85). The results from the primary efficacy endpoint showed that the estimated median TTP was 11.9 weeks for ZD6474 and 8.1 weeks for gefitinib. The estimated hazard ratio of 0.632 corresponds to 58% prolongation of TTP for ZD6474 compared with gefitinib (95% CI, 11–125%; $P = 0.011$). The adverse event profile of ZD6474 was similar to that seen in previous trials, and included rash (grade 1/2, 25.3%; grade 3/4, 4.8%), diarrhoea (grade 1/2, 48.2%; grade 3/4, 7.2%) and asymptomatic QTc prolongation (all grade 1, 21.7%). There were no unexpected safety findings with gefitinib-treated patients. Results from secondary endpoints in part A, including response rate and survival, will be presented. Part B of the study is ongoing.
Conclusions: In this population of NSCLC patients, ZD6474, an inhibitor of VEGFR and EGFR tyrosine kinase activity, produced a statistically significant improvement in TTP when compared with the EGFR tyrosine kinase inhibitor gefitinib. These results support conducting further confirmatory trials.
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Poster presentations (Mon, 31 Oct)
Lung cancer

1125 POSTER

Improved disease-free durvival and dverall durvival by Navelbine (N) and Cisplatin (P) as adjuvant chemotherapy in completely resected (Stage I-III) Non Small Cell Lung Cancer (NSCLC): ANITA Trial. On behalf of Adjuvant Navelbine International Trial Association

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We are reporting the final results of a large randomized phase III trial (ANITA) demonstrating a survival benefit of vinorelbine-cisplatin as adjuvant chemotherapy for completely resected NSCLC pts. The ANITA study was designed to evaluate the impact on survival of adjuvant NP compared to observation in completely resected NSCLC pts.
Methods: completely resected pts were randomized to receive four cycles of adjuvant NP (N 30 mg/m^2/week for consecutive 16 weeks in combination with P 100 mg/m^2 on d1 every 4 weeks) or observation. Pts had to have histologically proven stage I (T2N0 only), II and IIIA NSCLC. Postoperative radiotherapy was predetermined by each center. ANITA was a multicenter, randomized (1:1) study, stratified by center, stage and histology. The main study end point was overall survival, assuming 5% alpha error and 90% power to achieve a 10% improvement on survival at 2 years, 400 pts had to be enrolled in each arm.
Results: Between 12/94 and 12/00, 840 pts (NP: 407, observation 433) were randomized from 101 centers in 14 countries. Median age 59 years (range 18–75), male 86%, WHO PS 0–1 95%, squamous cell carcinoma 59%, stage I, II, IIIA were 35%, 30% and 35% respectively. Lobectomy was performed in 58%, and pneumonectomy in 37%. Groups were well balanced with regards to age, gender, stage, histology and resection type. After a median follow-up >70 months, Overall and relapse-free survival were significantly different between arms; 65.8 and 36.3 months for NP versus 43.7 and 20.7months for observation (p value were 0.0131 and 0.002 respectively). Two, 5 and 7-year survivals were 68%, 51% and 45% in the NP arm versus 63%, 43% and 37% in the observation arm. The 5-year survival for stage I, II, IIIA were 62%, 52% and 42% in the NP arm versus 63%, 39% and 26% in the observation arm. The toxicity in the NP arm (WHO grade 3–4) was as expected and manageable; neutropenia 85%, febrile neutropenia 12.5%, nausea-vomiting 27%, constipation 5%, and peripheral neuropathy 3%. Seven pts (1.7%) died of drug-related toxicity. Cox Multivariate Analysis reported that Negative Nodal Status, Stage IB/II, Age <55yrs and chemotherapy were favorable prognostic factors for survival.
Conclusion: The ANITA results show that NP significantly improves relapse-free and long-term survival in completely resected NSCLC patients.

1126 POSTER

Symptom relief in patients with non-small cell lung cancer (NSCLC) after treatment with paclitaxel poliglumex (PPX, XYOTAX™): phase III trial results

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Background: Paclitaxel poliglumex (PPX; XYOTAX™) is a macromolecular drug conjugate linking paclitaxel to a biodegradable polymer, poly-L-glutamic acid. Because poly-L-glutamic acid links to the 2' hydroxyl of paclitaxel, a site crucial for tubulin binding, an inactive polymeric conjugate is formed. PPX is relatively stable in plasma; more than 97% of paclitaxel in circulation is present as the inactive conjugate thereby reducing systemic exposure to high concentrations of free paclitaxel. Consequently, PPX may have a more favorable toxicity profile than standard paclitaxel and improve symptom relief. Phase I/II studies indicate that PPX is active and generally well tolerated in high-risk patients (>70 years of age or poor performance status). Recently, enrollment has completed in 2 phase III trials examining single-agent PPX in patients with advanced NSCLC (STELLAR 2 and 4); the current analysis reports on patient benefit and symptom relief.
Materials and methods: STELLAR 2 included 849 patients and compared PPX to docetaxel in NSCLC patients with disease progression on or after a single platinum-containing regimen; STELLAR 4 included 477 poor performance status (PS2) patients and compared PPX to gemcitabine or vinorelbine. Patient reported symptoms were measured using FACT-LCS, a validated tool that consists of 7 questions that assess symptoms commonly reported by patients with lung cancer. FACT-LCS questions are rated on 5-point Likert-type scales ranging from 0 = "Not at All" to 4 = "Very Much." Patients completed the questionnaire within 3 days before each study treatment and 3 weeks after the last study dose. FACT-LCS response criteria were defined by exposure to drug and the change in FACT-LCS score from baseline over time: Worsened (2 or more point decline); Improved (2 or more point increase); Stable (1 point change or less).
Results: Fisher's exact test for equal proportion of patients achieving at least a 2-point increase in FACT-LCS score from baseline to week 3 will be performed. The Wilcoxon rank-sum test will be performed to assess change in FACT-LCS score from baseline over time. Summary statistics and 95% CI for the mean will be provided for each treatment arm at the scheduled visit week of the FACT-LCS questionnaire.

1127 POSTER

Phase II study of the EGFR tyrosine kinase inhibitor erlotinib in patients >70 years of age with previously untreated advanced non-small cell lung carcinoma

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Background: Chemotherapy for patients ⩾70 with advanced NSCLC is associated with survival benefits but with increased toxicity. Erlotinib has shown promising activity, and a tolerable side effect profile, in the treatment of patients who have failed prior chemotherapy. We have conducted a single center, phase II trial of erlotinib in patients ⩾70 years with previously untreated advanced NSCLC.
Methods: Patients who were chemotherapy-naïve, IIIB/IV, PS 0–2, were enrolled and treated with erlotinib, 150 mg p.o.q.d, until evidence of disease progression or toxicity. Median survival is the primary endpoint. Secondary endpoints include response rate, toxicity, quality of life (measured by LCSS), and gene sequencing for EGFR and K-ras mutations, and EGFR copy number (CN).
Results: From 3/03 to 2/05, 76 patients were treated; all were evaluable for survival and toxicity; 66 were evaluable for response. Demographics: M/F: 40/36; median age 75 (range 70–91); PS 0/1/2 13/55/8. Pathology: adenocarcinoma 51%; squamous 9%; adenocarcinoma with BAC features 8%; BAC 4%; other 28%. Smoking status: current/former/never: 4/64/8. Toxicity: Rash 75% (grade 1/2: 88%, grade 3:12%; grade 4: 0%); diarrhea 61% (grade 1/2: 98%; grade 3: 2%; grade 4: 0%). Other ⩾grade 3 toxicities: interstitial pneumonitis 3/76; anorexia 1/76; dehydration 2/76; hand–foot syndrome 2/76; elevations in PT/PTT 2/76; GI bleeding 2/76; hemoptysis

1/76; hypokalemia 1/76. Nine patients were discontinued from study due to toxicity. There was one treatment-related death (pneumonitis). Response: CR 0, PR 8 (12%; 95% CI 5–23%), SD 32 (48%; 95% CI 37–60%), and PD 26 (39%; 95% CI 28–51%). Median duration of PR has not been reached. Median duration of SD was 6 months. Survival: Median overall survival was 11.0 months (95% CI 8–14 mo). Median survival by response: PR: median survival not yet reached; SD: 12 mo (95% CI 10–16 mo); PD: 7 mo (95%CI 4–11 mo). In 28 pts with available tissue, EGFR mutations were found only in 3/5 responders. K-ras mutations were found in 2/9 with disease progression and 2/13 with stable disease. EGFR CN did not correlate with treatment outcome.
Conclusions: Erlotinib appears to be relatively well tolerated and demonstrates encouraging activity and median survival in patients $\geqslant$70 years of age with previously untreated advanced NSCLC. We have recently completed accrual, and results will be updated.

1129 POSTER

Sequential versus concomitant administration of docetaxel and gemcitabine as first-line treatment of advanced non-small cell lung cancer (NSCLC): results of a phase II/III randomised study

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Background: Docetaxel (D) and gemcitabine (G) – alone or in combination – have shown encouraging activity and relatively favourable toxicity in patients (pts) with advanced NSCLC. However, the optimum schedule requires definition. This Phase II/III study evaluated the clinically relevant haematological toxicity (CRHT) of first-line treatment with G and D given either concomitantly or sequentially. Interim results have been presented previously (J Clin Oncol 2005; 23: 634S [abstract 7057]).
Methods: Pts were randomised to receive 3-weekly cycles of G 1000 mg/m^{2}and D 75 mg/m^2 either concomitantly (Arm A: G, Days 1, 8 and D, Day 8 for 6 cycles) or sequentially (Arm B: G, Days 1, 8 for 3 cycles followed by D, Day 1 for 3 cycles). CRHT was defined as NCI-CTC Grade 3–4 thrombocytopenia requiring platelet transfusion, anaemia requiring red blood cell transfusion or febrile neutropenia requiring intravenous (iv.) antibiotics.

	Arm A, G + D (N = 166) n (%)	Arm B, G → D (N = 160) n (%)
CRHT		
At least one event	26 (16)	8 (5)
Anaemia + transfusion	19 (11)	8 (5)
Thrombocytopenia + transfusion	2 (1)	1 (1)
Febrile neutropenia + iv antibiotics	7 (4)	1 (1)
Overall Grade 3–4 haematological toxicity		
At least one event	67 (40)	46 (29)
Anaemia	7 (4)	3 (2)
Thrombocytopenia	10 (6)	4 (3)
Neutropenia	61 (37)	42 (26)

Results: The Phase II study included 339 pts; data from 336 pts are reported in this abstract (Arms A/B: 174/162 pts; median age 62.1/64.9 years). Arms were well matched for standard demographics. At baseline, 87% of pts had stage IV disease; 85% had WHO PS $\leqslant$ 1. Median survival was 7.1 and 7.2 months in Arms A and B, respectively ($p > 0.05$); overall response was 32% and 23%, respectively ($\div^2$ test, $p = 0.097$) and median time to progression was 6.2 and 4.7 months, respectively (log-rank test, $p = 0.016$). Arm B received 64% and 44% of the total doses of G and D, respectively, given in Arm A. CRHT occurred less often in Arm B ($p = 0.002$): the proportion of patients with CRHT was 31% of those with CRHT in Arm A. Transfusions and iv antibiotic treatment days were less common in Arm B (Table, 326 evaluable pts). QoL (EORTC-LC13 and SS14 measurements) also favoured Arm B. Final Phase II analysis results for 339 patients will be presented.
Conclusion: G and D given sequentially is as effective as concomitant administration of G and D as first-line treatment for advanced NSCLC, and is associated with significantly reduced CRHT, less iv antibiotic use and a trend towards improved QoL.

1130 POSTER

Docetaxel/gemcitabine vs. a sequential protocol comprising cisplatin/gemcitabine/docetaxel in the first-line treatment of patients with stage IV non-small cell lung cancer (NSCLC): results of a randomised phase II trial

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Background: Patients with metastatic non-small cell lung cancer (NSCLC) are most frequently treated with a platinum-based chemotherapy doublet combination. However, recent studies have demonstrated that triple-agent therapies allow improvement in the treatment response but can be associated with frequent intolerability. A sequential triple-agent schedule may combine acceptable tolerability and good efficacy. We therefore conducted a multicentric, prospectively randomised study that evaluates a sequential three-drug schedule and a platinum-free doublet regimen.
Methods: Patients with histologically confirmed metastatic (UICC stage IV) NSCLC were randomised to one of two protocols: gemcitabine (900 mg/m^2, 30 min. infusion) on days 1 and 8, and docetaxel (75 mg/m^2, 1 hour infusion) on day 1, repeated every three weeks up to six cycles (DOC-GEM). In regimen CIS-GEM-DOC, gemcitabine (900 mg/m^2, days 1 and 8) and cisplatin (70 mg/m^2, 1 hour infusion, day 1) were given for three cycles, followed by three cycles of docetaxel (100 mg/m^2, day 1, every three weeks).
Results: 113 patients (pts.) were totally included. 55/58 pts. were randomised to DOC-GEM and CIS-GEM-DOC, respectively. One patient was excluded from analysis due to violation of inclusion criteria. 20.4% of the pts. responded in the DOC-GEM arm whereas 31.0% responded in the CIS-GEM-DOC protocol (intent-to-treat, WHO criteria, difference not significant). The median time to progression was 3.6 months for patients receiving DOC-GEM (95% confidence interval 1.4 to 5.9) and 5.2 months in the CIS-GEM-DOC schedule (95% confidence interval 3.1 to 7.3, $p = 0.06$). The median survival was 8.7 months with DOC-GEM (95% confidence interval 5.7 to 11.6) and 9.4 months for patients receiving CIS-GEM-DOC (95% confidence interval 7.8 to 11.0, difference not significant). The 1-year survival rates were 34% and 35%, respectively. Mild to moderate leukopenia was frequently seen in both schedules. Other frequent adverse effects were nausea/vomiting, thrombocytopenia, anemia, diarrhea, and skin toxicity.
Conclusions: In the present study, both schedules demonstrated good efficacy and acceptable toxicity. No significant differences were demonstrated in terms of response rate or survival. However, the sequential triple-agent schedule approached statistical significance in response duration.

1131 POSTER

Addition of CPG 7909 to taxane/platinum regimen for first-line treatment of unresectable NSCLC improves objective response in phase II clinical trial

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Background: A taxane/platinum regimen remains first-line treatment of stage IIIb/IV (unresectable) non–small cell lung cancer (NSCLC), yet expected partial response is only 20%-30%. Tumor response and survival have been significantly improved in many preclinical models with the addition of synthetic oligodeoxynucleotide CPG 7909, a Toll-like receptor 9 agonist with immunostimulatory activity. Previous trials have established the dosing ranges, biologic response, and safety of weekly subcutaneous CPG 7909.
Materials and Methods: To investigate the effect of adding CPG 7909 to standard chemotherapy for first-line treatment of stage IIIb/IV NSCLC,