73%, squamous histology 48%, WHO performance status 0 55%, stage I 61%, stage II 32% and stage III 7%. In the CT-S group 75% patients received all 3 prescribed cycles of chemotherapy, 13% received 2 cycles, 7% 1 cycle and 4% no chemotherapy. Pre-chemotherapy the proportions of patients reported as having cough, breathlessness, haemoptysis, and chest pain were 62%, 46%, 21%, and 20% and post-chemotherapy the proportions were 39%, 33%, 2%, and 9% respectively. During chemotherapy the following proportions of patients were reported as experiencing moderate/severe symptoms: 29% lethargy, 28% nausea, 17% alopecia, 12% anorexia, 11% vomiting, 11% sore mouth and 6% ototoxicity. Three patients died within 30 days of a cycle of chemotherapy (2 myocardial infarctions, 1 lung cancer). Post-chemotherapy and pre-surgery 47% patients were reported as having responded (3% CR, 44% PR), 27% patients had stable disease, only 2% showed progressive disease, and 23% were not assessable. In the S group the median time from randomisation to surgery was 16 days, compared to 84 days in the CT-S group (medians of 7 days from randomisation to start of chemotherapy, 63 days on chemotherapy, and 14 days from the end of chemotherapy to surgery). Disease stage based on clinical TNM reported at randomisation and pathological TNM reported at surgery were compared, for 175 S and 172 CT-S patients with data at both timepoints. In the S group 19% were reported as having a lower (better) pathological stage, 45% the same, and 36% a worse stage. In the CT-S group the respective proportions were 31%, 41% and 28%. The extent of surgery was similar in the 2 treatment groups: lobectomy 50% S, 53% CT-S, pneumonectomy 29% S, 27% CT-S, other resections 9% S, 8% CT-S, thoracotomy with no resection 4% S, 3% CT-S, and no surgery 7% S, 10% CT-S.
Conclusions: In this trial, giving 3 cycles of cisplatin-based chemotherapy appeared to be feasible and generally well tolerated and few patients progressed on chemotherapy.

1122 ORAL

Paclitaxel poliglumex vs. gemcitabine or vinorelbine for the treatment of performance status (PS) 2 patients with chemotherapy-naïve advanced non-small cell lung cancer (NSCLC): the STELLAR 4 phase III study

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Background: Platinum-based chemotherapy is standard of care for patients with advanced NSCLC; however, this treatment is usually avoided in patients with poor PS due to the associated toxicities that can exacerbate pre-existing co-morbidities. These patients are usually treated with single agents and no standard treatment has been established. Paclitaxel poliglumex (PPX; XYOTAX™) is a macromolecular drug conjugate linking paclitaxel with a biodegradable polymer, poly-L-glutamic acid. Phase I/II studies indicated that PPX is active and generally well-tolerated in high-risk patients (PS2 or >70 years). This study compares PPX vs. gemcitabine or vinorelbine in chemotherapy-naïve PS2 patients with advanced NSCLC.
Patients and methods: This randomized, open-label, multinational, phase III study included chemo-naïve PS2 pts with locally-advanced or metastatic NSCLC not amenable to combined modality therapy with curative intent or recurrent disease previously treated with radiation and/or surgery. Pts were randomized equally to either: (A) PPX 175 mg/m^2 Q3W (210 mg/m^2 before Amendment 3); or (B) gemcitabine 1000 mg/m^2 (days 1, 8, 15 Q4W) or vinorelbine 30 mg/m^2 (days 1, 8, 15 Q3W). Stratifications included gender, geographic location, disease stage, history of brain metastases. Treatment continued until completion of 6 cycles, disease progression or intolerable toxicity. The primary endpoint was overall survival (OS). Secondary endpoints included RR, TTP, toxicity, and QOL.
Results: A total of 477 pts enrolled; median age was 63 (range: 30–90), 72% were male, and 68% had stage IV disease. Treatment with PPX resulted in a median survival of 7.3 months and a 1-year and 2-year survival of 26% and 15%, respectively. The control arm showed a median survival of 6.6 months, and 1-year and 2-year survival of 13% and 10%, respectively. The difference in survival was not statistically significant. When PPX was compared to gemcitabine, the survivals were comparable; PPX compared to vinorelbine showed a significant improvement in survival, gemcitabine also showed a survival benefit over vinorelbine ($p < 0.02$ for both). More pts ($p = 0.003$) completed full 6 courses of therapy on the PPX arm compared to the control arm. In the PPX arm, there were fewer cardiac toxicities ($p = 0.013$), gastrointestinal side effects ($p = 0.004$), nausea ($p = 0.041$), and vomiting ($p = 0.013$). PPX pts also had a significant reduction in severe hematologic toxicities including anemia ($p < 0.001$), neutropenia ($p = 0.006$), and thrombocytopenia ($p = 0.003$). Hair loss was uncommon on both arms. Grade 3/4 neuropathy was observed more frequently on the PPX arm (4% vs. 0%).
Conclusions: Compared to the current single-agent standards in NSCLC, gemcitabine and vinorelbine, PPX is less toxic, and provides a more convenient treatment schedule. PPX has a comparable efficacy compared to gemcitabine and a survival benefit compared to vinorelbine.

1123 ORAL

Panitumumab, a fully human antibody, combined with paclitaxel and carboplatin versus paclitaxel and carboplatin alone for first line advanced non-small cell lung cancer (NSCLC): a primary analysis

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Background: Panitumumab is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFr). In part 1 of this 2-part phase 2 trial in patients (pts) with advanced NSCLC, panitumumab could be safely combined with standard paclitaxel (P; 200 mg/m^2) and carboplatin (C; 6 mg/min/mL) (Crawford, ASCO 2004).
Methods: In Part 2, pts (stage IIIB or IV NSCLC, EGFr expression $\geqslant$1+ in 10% of tumor cells, ECOG <2) were randomized 2:1 to receive panitumumab 2.5 mg/kg QW plus PC Q3W (Arm 1) or PC alone Q3W (Arm 2). PC was continued until PD or up to a maximum of 6 cycles, panitumumab was continued until PD or intolerability. Tumor response (RECIST) was evaluated Q6W. The primary study objective was to compre time to PD (TTP) with panitumumab + PC vs PC alone; secondary objectives were to compare additional measures of efficacy and safety. The primary analysis was performed when 113 PD events occurred and had 65% power at the $p = 0.10$ level to detect a 50% improvement in TTP.
Results: of 175 pts enrolled, 166 treated pts (112 in Arm 1; 54 in Arm 2) were included in this analysis. Baseline demographics and disease characteristics were similar between arms. The study included 94 men and 72 women (mean [SD] age of 61.5 [10.4] yrs, ECOG of 0 [n = 52] or 1 [n = 112]). Two percent were Asian; 10% never smoked. Most (62%) had adenocarcinoma; 21% had squamous cell carcinoma. Median TTP (95% CI) was 4.2 (3.1, 5.4) mos for Arm 1 and 5.3 (3.6, 5.6) mos for Arm 2 (log-rank $p = 0.55$). Objective response rates were 15.2% for Arm 1 and 11.1% for Arm 2 ($p = 0.63$). Median (95% CI) survival times were 8.5 (7.1, 12.0) mos for Arm 1 and 8.0 (6.7, 11.8) mos for Arm 2 ($p = 0.81$). Adverse events (Arm 1 vs Arm 2) more frequently seen in the panitumumab arm included rash (59% vs 17%), dry skin (20% vs 4%) dermatitis acneiform (21% vs 0%), pruritus (18% vs 6%), diarrhea (48% vs 26%), vomiting (44% vs 31%), stomatitis (33% vs 9%), dizziness (21% vs 11%). Neutropenia was not significantly different (24% vs 28%). No panitumumab-induced human anti-human antibodies were detected in 110 pts tested post baseline.
Conclusions: Results from this phase 2 study indicate that panitumumab + PC is well tolerated with similar efficacy as PC alone in an unselected NSCLC population. Retrospective assessment of tumors for biomarkers may define subpopulations more likely to benefit from panitumumab. Clinical studies of panitumumab in NSCLC are ongoing with other novel combinations of targeted agents.

1124 ORAL

Results of a randomized, double-blind Phase II trial of ZD6474 versus gefitinib in patients with NSCLC

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Background: ZD6474 is an orally available inhibitor of two key pathways in tumour growth: vascular endothelial growth factor receptor (VEGFR)-dependent tumour angiogenesis and epidermal growth factor receptor (EGFR)-dependent tumour cell proliferation and survival. In this ongoing two-part Phase II study, the efficacy and safety of ZD6474 is compared with that of gefitinib (IRESSA), an EGFR tyrosine kinase inhibitor approved for the treatment of advanced non-small-cell lung cancer (NSCLC).
Methods: Patients with locally advanced or metastatic (IIIB/IV) NSCLC, after failure of first-line and/or second-line platinum-based chemotherapy

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.
IRESSA is a trademark of the AstraZeneca group of companies

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