Lung Cancer

Oral presentations (Thu, 3 Nov, 8.30–10.30)
Lung cancer – NSCLC

1119 ORAL

Continuous hyperfractionated accelerated radiotherapy – weekend less (CHARTWEL) versus conventionally fractionated (CF) radiotherapy in non-small-cell lung cancer (NSCLC): first results of a phase III randomised multicentre trial (ARO 97-1)

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Background: Shortening of overall treatment time by accelerated radiotherapy has been shown to improve survival of patients with localised inoperable NSCLC in the CHART trial. This trial compared 54 Gy in 36 fractions of 1.5 Gy in only 12 consecutive days (CHART) with conventional fractionation (CF) to 60 Gy in 6 weeks. However also after CHART more than 80% of the patients developed local recurrences, calling for further intensification of local therapy. CHARTWEL (CHART weekend less) allows to escalate the total dose of highly accelerated radiotherapy. The present randomized phase III trial investigated whether CHARTWEL to 60 Gy improves outcome in patients with localized NSCLC compared with CF to 66 Gy which reflects a widely used standard for 3D conformal radiotherapy.
Patients and methods: 406 patients were randomised by 15 centres in Germany, Poland and Czech Republic between Sept. 1997 and Febr. 2005. Patients with NSCLC localised to the chest, performance status 0–1, with and without prior Chemotherapy (CTx) were included. Stratification criteria for randomisation were UICC stage, histology, prior CTx, and centre. CHARTWEL was applied in fractions of 1.5 Gy given three times per day on 5 days per week to a total dose of 60 Gy in 2.5 weeks. CF was applied in 36 fractions of 2.0 Gy, 5 fractions per week, to a total dose of 66 Gy in 6.5 weeks. All patients were treated using 3D conformal radiotherapy techniques at linear accelerators. Data in this abstract are from prelimary analysis at the end of accrual in February 2005. Formal analysis of the complete data set will be performed after retrieval of missing data in July 2005 and will be reported during the meeting.
Results: The groups were well matched for prognostic factors. Most patients suffered from locally advanced tumours (UICC I 10%, II 6%, IIIA 38%, IIIB 46%). Median follow-up is 47 months. Overall survival rates (main endpoint) at 1, 2 and 3 years were 55%, 32%, and 18% after CF versus 54%, 28%, and 21% after CHARTWEL (HR 0.99 [95% CI 0.79; 1.24]; p = 0.96). Disease free survival and local control (secondary endpoints) were also not significantly different in the treatment arms. Oesophagitis was more pronounced in the CHARTWEL arm but was clinically well manageable and resolved after treatment. Radiological signs of pneumopathy were increased after CHARTWEL, clinical symptoms of pneumonitis are currently being analysed.
Conclusions: Highly accelerated CHARTWEL radiotherapy to 60 Gy in 2.5 weeks was not superior to conventional fractionation to 66 Gy in 6.5 weeks in NSCLC localised to the chest. The data support a small time factor of fractionated radiotherapy in NSCLC since the higher dose in the CF arm was compensated by the shortening of overall treatment time in the CHARTWEL arm. Subgroup analysis awaits longer follow-up.
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1120 ORAL

A randomized trial of radical surgery (S) versus thoracic radiotherapy (TRT) in patients (pts) with stage IIIA-N2 non-small cell lung cancer (NSCLC) after response to induction chemotherapy (ICT) (EORTC 08941)

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Background: The optimal locoregional treatment – TRT or S – following systemic ICT of pts with stage IIIA-N2 NSCLC is unclear. 5-year survival rate in uncontrolled series of either modality varies between 5–25%.
Methods: selected pts with histological or cytological proven stage IIIA-N2 NSCLC were given 3 cycles of platinum-based ICT. Responding pts were then randomized between S: radical resection with lymph node dissection and optional postoperative radiotherapy (PORT), or TRT: at least 40 Gy in 2 Gy daily fractions on the mediastinum with a boost to at least 60 Gy on the involved field (IF). In order to observe an increase of 5-year overall survival (OS) from 15 (TRT) to 25% (S), 292 events out of 358 randomized pts had to be observed (log rank test, power 80%, type I error 5%). Secondary endpoints were progression free survival (PFS) and toxicity.
Results: ICT achieved an average response rate of 62% (95%CI: 58–66) among the 570 registered pts who started protocol treatment. Of these, 332 were randomized (167 to S and 165 to TRT), having the following characteristics: median age 61 years; male 74%; squamous/non-squamous: 40/60%; T1/2/3: 12/68/17%. In the 154 operated S pts, the following rates were observed: exploratory thoracotomy: 14%; radical resection: 50%; pathological downstaging: 42%; pathological complete response: 5%; operative mortality: 4%; PORT 40%. Among 154 pts randomized to TRT and actually irradiated, median total treatment time was 43 days (15–60). CT-scan planning was used in 92%. The median total dose delivered to the normal mediastinum/IF was 40/60 Gy, respectively. A grade 3/4 acute side effect of any kind occurred in 9% of irradiated TRT pts and 1 patient died of radiopneumonitis. With a median follow up of 72 months, median and 5 year OS for pts randomized to S and TRT are 16.4 vs.17.5 months and16 vs. 13%, respectively (HR 1.08, 95% CI 0.84–1.35). Median and 2y PFS for pts randomized to S and TRT are 9.0 vs.11.3 months and 27 vs. 24%, respectively (HR 1.06, 95% CI 0.85–1.33). Subgroupanalysis shows lobectomy and mediastinal downstaging to be linked to better survival.
Conclusion: In selected pts with proven stage IIIA-N2 NSCLC and a response to ICT, S improves neither OS nor PFS in comparison to TRT.

1121 ORAL

The impact of giving neo-adjuvant chemotherapy for patients with non-small cell lung cancer (NSCLC): data from the MRC LU22/NVALT/EORTC 08012 randomised clinical trial

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Background: Patients with resectable NSCLC were randomised to receive either surgery alone (S) or 3 cycles of cisplatin-based chemotherapy followed by surgery (CT-S). On a patient by patient basis, chosen prior to randomisation, clinicians could choose to give MIC, MVP, cisplatin/vinorelbine, carboplatin/paclitaxel, carboplatin/docetaxel or cisplatin/gemcitabine. Using data from the first 500 patients randomised, this paper reports on the impact of neo-adjuvant chemotherapy in terms of its feasibility, toxicity, response rates, downstaging, and extent of resection. Survival endpoints will be reported when the required number of events (233) have been achieved.
Material and methods: Patients (252 S, 248 CT-S) were entered from 66 centres in the UK, the Netherlands, Germany and Belgium from July 1997 to Nov 2004.
Results: The main patient characteristics were well balanced between the 2 treatment groups at randomisation: median age 63 years, male

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