Significantly longer survival in pts treated with surgery was found in all T and N categories except N2 disease. Local relapse was more frequent in pts treated conventionally (55%) then in surgically (15%, p<0.001). Distant relapse rates were similar in both groups (36% and 40%, respectively). The most common site of metastases in the entire series was CNS followed by liver, lymph nodes, bones, lungs and skin.

We conclude, that surgery may have a positive impact on survival of LD SCLC pts, and a randomized study addressing this issue should be considered.

217 POSTER

Randomized, phase II study of topotecan/paclitaxel versus cisplatin/etoposide in patients with untreated, extensive disease, small cell lung cancer (SCLC)

H. Lena[1], J. Breton[2], W. Yu[3], K. Steppert[4], K. Lightcap[5], G. Ross[5], M. Lymboura[5]. [1] *Hospital Pontchaillou, Rennes, France;* [2] *Centre Hospitalier de Belfort, Belfort, France;* [3] *Princess Margaret Hospital, Kowloon, Hong Kong;* [4] *Bezirksklinikum Kutzenberg, Ebensfeld, Germany;* [5] *GlaxoSmithKline, Oaks, USA*

Topotecan and paclitaxel are active single agents in the treatment of SCLC. In previous phase II studies, the combination of topotecan and paclitaxel has demonstrated encouraging activity, suggesting that this combination is worthy of further investigation. This phase II study was designed to compare the combination of topotecan (T) and paclitaxel (Px) with the standard front-line therapy of cisplatin (P) and etoposide (E). Eligible patients had bidimensionally measurable disease, ECOG PS 0-2, and adequate bone marrow, hepatic and renal function. Asymptomatic brain metastases were allowed. Recruitment is completed with 151 patients randomized (76 on the TPx arm and 75 on the PE arm), and preliminary results are pending. Demographic baseline characteristics: females/males 36/115; median age 61; median PS=1; elevated LDH 66%. Patients were randomized to receive either TPx: T 1.0 mg/m2/d IV d 1-5 and Px 175 mg/m2 IV d 1 with prophylactic G-CSF 5ug/kg/d SC starting d 6 for all patients; or EP: P 80 mg/m2 IV d 1 with E 100-120 mg/m2 IV d 1-3. Cycles were repeated every 21 days. The primary efficacy variable is objective response rate, which is to be verified by independent, blinded radiologic review.

Response and tolerability data will be available by the time of the meeting.

218 POSTER

Cisplatin-epirubicin-paclitaxel (PET) weekly administration with G-CSF support in extensive SCLC. A SICOG phase II study

N. Panza, G. Frasci, G.P. Nicolella, P. Comella, L. Maiorino, D. Muci, A. Farris, A. Lamberti, E. Barbato, G. Comella. *SICOG c/o INT, Naples, Italy*

Background: In a previous phase I study (Frasci et al. Br J Cancer 2001 in press) we showed that cisplatin 40 mg/sqm, paclitaxel 85 mg/sqm and topotecan 2.25 mg/sqm could be safely given weekly in presence of G-CSF support, and that an 80% ORR can be achieved in advanced disease with this regimen.

Purpose: We tried to improve the efficacy of the treatment by increasing the dose of paclitaxel (from 85 to 120 mg/m2), and replacing topotecan with epirubicin (50 mg/m2/week). The dose of cisplatin was slightly decreased to 30 mg/m2/week. This regimen at the present doses had already been tested in a large number of breast cancer patients.

Patients and Methods: Patients with extensive SCLC, aged 18-70, with ECOG PS < 2 were considered eligible provided that they had not received prior chemotherapy. They received weekly P, E, and T at the above reported doses for a maximum of 12 cycles. G-CSF was given on days 3-5 of each week. The planned final sample size was of 33 patients, calculated according to the Simon two-stage design (end point was considered the CR, with a p1=30% and p0=10%), but a preliminary analysis was planned after 22 patients.

Results: As of April 9, 2001, 24 patients have been included in the study (median age 61; PS 0-1/2=13/11) for a total of 178 weekly cycles delivered. Twenty-three patients have been considered eligible for toxicity and response since in one case the hystotype resulted to be NSCLC after a careful revision.

Overall, grade 3-4 neutropenia and thrombocytopenia occurred in 7 and 3 patients. One patients died after 1 cycle due to cardiac failure probably related to sepsis. Anemia was the most frequent hematologic side effect, 9 patients requiring at least once red blood cell transfusions. Symptomatic thrombocytopenia was never observed. Nonhematologic side effects were in general moderate. Severe emesis, mild peripheral neuropathy and severe fatigue were observed in 2, 8, and 5 patients respectively. Among the 19 patients who completed at least 6 cycles 5 complete responses and 10 partial responses have been recorded for a 79% ORR [95% CI=54-94].

Conclusions: The cisplatin, epirubicin, paclitaxel regimen is well tolerated and highly active in extensive SCLC patients. The accrual continues until the planned sample size of 33 patients is reached.

219 POSTER

Activity of ZD0473 in small-cell lung cancer: an update in patients relapsing after one prior chemotherapy regimen

J. Schiller[1], P. Bonomi[2], M. Modiano[3], P. Cornett[4], M. Koehler[5]. [1] *University of Wisconsin Comprehensive Cancer Center, Madison, USA;* [2] *Rush-Presbyterian-St-Luke's Medical Center, Chicago, USA;* [3] *Arizona Clinical Research Center, Tucson, USA;* [4] *Veterans Affairs Medical Center, San Francisco, USA;* [5] *AstraZeneca, Wilmington, USA*

Aims: This Phase II multicenter study was conducted to assess the use of the new generation platinum drug, ZD0473, in patients with small-cell lung cancer who have previously failed one platinum-based chemotherapy regimen.

Methods: ZD0473 (120-150 mg/m2) was administered by a 1-h intravenous infusion on day 1 of each 3-week cycle. Patients were evaluated in two cohorts: (1) drug resistant (relapsed or progressed ≤8 weeks following prior chemotherapy); and (2) sensitive (relapsed or progressed beyond 8 weeks).

Results: In this ongoing trial, 38 patients with a median age of 62 years (range 38-80) have been recruited at present (F:M [15:23 patients]; resistant:sensitive [11:27]; performance status 0-1 [33] and 2 [5]). To date, 93 treatment cycles have been administered: median 2 cycles per patient (range 1-6), with 9 patients receiving ~4 cycles. Overall, 52 cycles were completed without dose reduction or delay, 12 cycles required dose reduction of >20%, and 13 cycles had a delay of ~7 days. Grade 3 or 4 hematologic toxicities (Common Toxicity Criteria) included thrombocytopenia (grade 3 [7 patients]; grade 4 [9]) and neutropenia (grade 3 [7]; grade 4 [1]). The most frequent grade 3 or 4 non-hematologic event was dyspnea (grade 3 [4]), irrespective of causality. Two patients withdrew due to hematologic toxicity. Response to treatment was evaluable in 6 resistant patients: 1 patient had a partial response and 5 patients had progressive disease. Of 21 evaluable sensitive patients, 2 patients had a partial response, 11 had stable disease (including 6 with some evidence of tumor shrinkage) and 8 had disease progression. Across the entire study population, 7 patients had an improvement in WHO score at endpoint. To date, 10 of 25 patients have died due to disease progression. Updated survival data will be presented.

Conclusion: ZD0473 had a manageable tolerability profile and there was a favorable response to treatment in terms of tumor response and stable disease, in both platinum-sensitive and -resistant patients.

220 POSTER

Paclitaxel and Gemcitabine for refractory or relapsed small cell lung cancer (SCLC). A multicentric phase II study

M. Domine[1], J. Gonzalez Larriba[1], R. Garcia Gomez[1], S. Morales[2], D. Isla[2], C. Garcia Giron[3], I. Maestu[3], V. Giner[4], S. Terrasa, J. Andrade[4], R. Alfonso, F. Lobo [5]. [1] *Fundacion Jimenez Diaz, Hospital Clinico, Hospital Gregorio Marañon, Oncologia, Madrid, Spain;* [2] *Hospital Arnau de Vilanova, Lleida, Hospital Clinico, Oncologia, Zaragoza, Spain;* [3] *Hospital General Yague, Burgos, Hospital Virgen de los Lirios, Oncologia, Alcoy, Spain;* [4] *Hospital Sagunto, Hospital Son Dureta, MallorcaHospital Virgen Salud, Oncologia, Toledo, Spain;* [5] *Hospital Clinico, Universitario Fundacion Jimenez DÃaz, Oncologia, Madrid, Spain*

Paclitaxel and gemcitabine have shown activity in SCLC, as single agent or in combination with others drugs, in untreated and even pretreated patients. Paclitaxel ® gemcitabine seems to be an attractive combination to explore in SCLC. We conducted a prospective phase II study to determine the activity of this combination as second line treatment in SCLC.

Patients and Methods: Patients were eligible if they had measurable or evaluable disease, performance status (ECOG) 0-2 and adequate hepatic, renal and bone marrow function. Paclitaxel dose was 175 mg/m2 (3 hour infusion)on day 1 and gemcitabine 1250 mg/m2 (30 minute infusion)on days 1 and 8. Cycles were administered every 3 weeks.

Results: 41 pts were enrolled, 37 male and 4 female. Median age was 62 years (range 42- 79); 83% had PS 0 or 1 and 17% PS 2; 17 pts had refractory disease (defined as progression within 3 months of starting

first-line treatment) and 24 pts had sensitive disease. A total of 154 courses have been administered (median 4 per patient).

To date 41 pts were evaluable for toxicity and 35 for response. Response rate (RR) was 48.8%, no complete responses were observed. 20% of pts showed stable disease (SD) and 31.5% progression (PD). The RR in refractory disease was 43%, SD 14% and PD 43%. In sensitive disease RR was 52%, SD 24% and PD 24%. The median duration of response was 3.7 months (95% C.I: 2.2 ± 8.8 m) and median time to progression 4.9 months (95% C.I: 4.1 ± 10.1 m) and median survival 7.1 months (95% C.I: 2.3 ± 7.1m).

Grade 3/4 neutropenia, anemia and trombocytopenia were observed in 7.5%, 2.5% and 5% of the patients respectively. Non-hematological toxicity was very mild. Grade 3 alopecia was observed in 25% of pts, grade 3 nausea/vomiting in 2.5%, grade 2 peripheral neuropathy in 6% and grade 2/3 skin toxicity in 5%.

Conclusions: This combination shows an encouraging activity in sensitive and even in refractory patients Toxicity is moderate and manageable. Further development of this combination is warranted in both untreated and pretreated patients.

221 POSTER

The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5-year follow-up

R.M. Bremnes[1], S. Sundstrøm[2], S. Kaasa[2], S. Aamdal[3]. [1] *University Hospital of Tromsø, Dept Oncology, Tromsø, Norway;* [2] *University Hospital of Trondheim, Dept Oncology, Trondheim, Norway;* [3] *The Norwegian Radium Hospital, Dept Oncology, Oslo, Norway*

Purpose: Demographic, clinical and laboratory parameters at the time of diagnosis have clinical significance. In a prospective study, we investigated the prognostic value of 22 pretreatment attributes in 436 small cell lung cancer (SCLC) patients.

Methods: Pretreatment clinical and laboratory parameters were registered at time of diagnosis [Age, gender, disease extent, ECOG performance status (PS), weight loss, erythrocyte sedimentation rate (ESR), haemoglobin level (Hgb), total WBC count, platelet count, serum g-glutamyl transferase (gGT), serum alkaline phosphatase (ALP), serum lactate dehydrogenase (LDH), neuron-specific enolase (NSE), serum sodium, number of metastases, and metastasis to seven different sites]. The minimum follow-up was 5 years. The prognostic value of the different variables was evaluated by univariate analysis (log rank test) and by the Cox multivariate regression model.

Results: Among all patients, the univariate analysis found gender, disease extent, PS, weight loss, ESR, Hgb, WBC count, platelet count, gGT, ALP, LDH, NSE, serum sodium, no. of metastases, adrenal metastasis, lung metastasis, bone metastasis, liver metastasis, and brain metastasis to be significantly associated with survival. The multivariate Cox model identified gender, disease extent, PS, weight loss, platelet count, LDH, and NSE as independent prognostic factors. In subset multivariate analyses performed according to extent of disease, PS, Hgb, WBC count, and NSE were identified as significant prognostic indicators for survival in limited-stage disease, while PS, weight loss, LDH, no. of metastases, liver metastases, and brain metastases were independent prognostic factors in extensive-stage disease. A significant correlation between serum LDH and NSE levels was observed.

Conclusion: Overall, gender, disease extent, PS, weight loss, Hgb, WBC count, platelet count, LDH, and NSE were found to be independent prognostic factors for SCLC survival. The prognostic value of these factors depends, however, highly on whether all SCLC patients or subsets of these are studied.

222 POSTER

Phase II study of sequential dose-dense paclitaxel followed by topotecan in extensive small-cell lung cancer (SCLC)

L. Santome, E. Felip, R. Rosell, M. Domine, A. Font, P. Garrido, A. Carrato, J. Terrasa, J. Mañe, J. Baselga.

Purpose: Patients (pts) with extensive SCLC have a poor pronostic. New therapeutic approaches are needed. In this phase II study paclitaxel and topotecan have been combined sequentially in a dose-dense schedule in chemonaive pts. These two drugs were chosen on the basis of their single-agent activity in previously untreated SCLC pts and because high doses of these agents could be administered in a dose-dense fashion.

Patients and Methods: Pts with untreated extensive SCLC received 3 cycles of paclitaxel 250 mg/m2 over 3 hours given at 14-day intervas folowed by 3 cycles of topotecan 2.5 mg/m2 x 5 days given every 21 days. Prophylactic filgastrim (G-CSF) was given. Pts progressing during the paclitaxel or topotecan and those not achieving complete response at completion of the full sequence subsequently received etoposide/cisplatin for 4 cycles. Between July 2000 and March 2001, 42 pts had been included (30 have completed chemotherapy tratment). Pts characteristics: median age 58 yr; 96% males; PS 0/1/2 in 9/27/5 pts.

Results: After paclitaxel, 53% (16/30 pts) had response; 26.6% (8/30 pts) stable disease (SD), and 20% (5/30) progressive disease. No pts were hospitalized due to febrite neutropenia during paclitaxel treatment and a 30% developed grade II peripheral neuropathy. Twenty-one pts that responded or had SD to paclitaxel received topotecan. Toxicites due to topotecan included febrile neutropenia in 5/30 pts (24%) with one toxic death and 5/21 (24%) needed blood product transfusion. Nonhematologic toxicities were frequent but mild. The median survival time was 10.5 months and the median progression free survival was 8 months.

Conclusion: Sequential dose-dense paclitaxel folowed by topotecan is well tolered and appears to be a higly active regimen in extensive SCLC.

Clinical pharmacology

223 POSTER

Renal safety of ibandronate 6 mg intravenously administered with shortened infusion times (15 and 30 minutes) in human volunteers: higher peak concentrations do not result in adverse renal effects

G. Neugebauer[1], W. Köhler[1], L. Akinkunmi[2], J. Pinner[3], H. Kletzl[4], L. Banken[4]. [1] *Roche Pharma Development, Mannheim, Germany;* [2] *LCG Bioscience, Bourn, Cambridge, UK;* [3] *Roche Pharma Development, Welwyn, UK;* [4] *Roche Pharma Development, Basel, Switzerland*

Background: Intravenous bisphosphonate administration has been associated with renal toxicity, as seen with tubular damage in preclinical investigations, elevated serum creatinine (zoledronate), and rare events of acute renal failure in clinical trials. Toxicity may be associated with the total dose administered or also with the peak concentrations achieved. The current investigation was conducted to determine if shortening of infusion time and thus increasing peak concentrations of an established safe dose of ibandronate is accompanied by any signs of early renal toxicity. In addition, the pharmacokinetics of the different infusion regimens were investigated.

Patients and Methods: Single infusions of 6 mg ibandronate administered within 60 (reference with demonstrated safety in Phase III trial), 30 or 15 min were investigated in parallel groups of 20 volunteers. Renal safety was monitored prior to and up to 3 days after infusion by measuring creatinine clearance and markers of tubular or glomerular damage (urinary excretion of albumin, alpha1- and beta2-microglobulin, and N-acetyl-beta-D-glucosaminidase [NAG]). Plasma and urine concentrations were determined at selected time points up to 28 h.

Results: With shortening of the infusion time, peak ibandronate concentrations increased from 307.9 ± 44.8 ng/mL (60 min) to 383.9 ± 41.3 ng/mL (30 min) and 396.7 ± 94.5 ng/mL (15 min). Serum creatinine concentrations and creatinine clearance were not changed by ibandronate and were not different between the three groups. Albumin, alpha1- and beta2-microglobulin, and NAG were also similarly unaffected by ibandronate infusion with any infusion time.

Conclusion: The increase of mean peak concentrations of ibandronate from 300 ng/mL (range 237-417) to about 400 ng/mL (range 227-582) did not lead to any adverse acute renal effects. Ibandronate 6 mg may be safely administered by a 15-min infusion. Infusions every 3 to 4 weeks can be viewed as separate single administrations from a pharmacokinetic viewpoint and should therefore provide the same safety profile. This should be confirmed in clinical studies using multiple administrations.