similar efficacy to that of intravenous NVB with a dose-equivalence between both formulations demonstrated from pharmacokinetics (PK). The safety profile is almost identical with the exception of more frequent nausea and vomiting, but rarely severe. In order to evaluate the impact of a standard anti-emetic prophylaxis, we compared the UGT toxicity in two NSCLC patient populations treated by oral NVB with/without anti-emetic prophylaxis.

Material and methods: The UGT has been retrospectively analysed from two studies performed in locally advanced or metastatic NSCLC pts receiving NVB oral as a weekly monotherapy at 60mg/m2 for 3 doses, then increased to 80mg/m2 in the absence of grade 3-4 neutropenia. In the 1st study (Ann Oncol 2001;12(10):1375-81), there was no anti-emetic prophylaxis given to the 76 pts treated with oral NVB. In the 2d protocol recently conducted in 56 pts, a systematic anti-emetic prophylaxis was recommended including 5–HT3 antagonists. PK was performed in both studies.

Results: In the 76 NSCLC pts (median age: 64y) without anti-emetic prophylaxis (1st study), nausea and vomiting (CALGB scale) were 83% and 65% respectively; however grade 3-4 were infrequent (10.5% and 7.9% respectively). Median delay between dosing and vomiting was 5 hours with only one occurrence within the 1st hour and 25% vomiting occurring between 2 and 3 hours post dose. Secondary prophylaxis was given to 49% pts (34% with a dopamine antagonist and 14.5% with a 5HT3 antagonist). In the 56 pts (2d study) (median age: 74y) with anti-emetic prophylaxis, 88% received a 5HT3 antagonist. Overall incidence of nausea (54%) and vomiting (24%) were largely reduced compared to their occurrences in the 76 pts without anti-emetic prophylaxis. One pt had grade 3 nausea (2%) and 1 pt (2%) grade 3 vomiting (NCI-CTCv2 scale). No influence of early vomiting (<3h) on NVB oral bioavailability was demonstrated from population PK analysis. The absence of any PK drug-drug interaction between anti-emetics and NVB oral was also well established.

Conclusions: UGT can be controlled in pts treated with oral NVB by a primary anti-emetic prophylaxis with 5HT3 antagonist. This type of prophylaxis is a standard recommendation in the ESMO guidelines. Moreover, neither early vomiting nor associated anti-emetic prophylaxis modify NVB blood exposure.

802 POSTER

Multicenter Phase II trial of weekly Taxol and Paraplatine as first line treatment in elderly patients with non small cell lung cancer (NSCLC): preliminary results

J.-L. Pujol[1], B. Milleron[2], E. Quoix[3], A. Depierre[4], J.-L. Breton[5], R. Gervais[6], D. Debieuvre[7], S. Hominal[8]. [1] *Hopital Arnaud de Villeneuve, Pneumologie, Montpellier, France;* [2] *Hopital Tenon, Pneumologie, Paris, France;* [3] *Hopital Civil, Pneumologie, Starsbourg, France;* [4] *Hopital Jean Minjoz, Pneumologie, Besancon, France;* [5] *Centre Hospitalier de Belfort, Pneumologie, Belfort, France;* [6] *Centre Francois Baclesse, Pneumologie, Caen, France;* [7] *Centre Hospitalier de Vesoul, Pneumologie, Vesoul, France;* [8] *Centre Hospitalier d'Annecy, Pneumologie, Annecy, France*

The use of platinum based chemotherapy in elderly patients with NSCLC is still controversial. The purpose of this phase II trial was to evaluate the efficacy and the safety of 1st line weekly Taxol (T) [paclitaxel] and Paraplatine (P) [carboplatin] in elderly patients with NSCLC.

Eligibility criteria included: age > or = to 70; measurable disease; ECOG PS 0-2; adequate bone marrow, liver, and renal function; no previous chemotherapy; and patient informed consent.

Treatment schedule: T 90 mg/m^2 IV (1h) on days 1, 8 and 15 and P AUC 6 IV on day 1 of a 28-day cycle. Tumor response was evaluated using RECIST criteria and symptoms were evaluated using lung cancer symptoms scale (LCCS).

Results: From March 2002 to March 2003, 51 patients have been included. Data are available for the 40 first patients. They were 29 males and 11 females, median age 74 (range 70-88), ECOG PS: 0 (33%), 1 (56%) and 2 (10%). Tumor histology was squamous cell carcinoma in 13 pts, adenocarcinoma in 23 pts, Large cell Carcinoma in 2. NSCLC was stage IV in 33 pts and IIIb in 7 pts. A total of 156 cycles have been administered (median 4 /pt [range 1-6]). Hematologic toxicity: G3-4 neutropenia in 2 pts (5%) G4 thrombocytopenia in 1 pt (3%) and G3 infection in 2 pt (5%). Non-hematologic toxicity: G3 asthenia in 1 pt (2%), G3 neuropathy in 3 (7%). One toxic death is reported. Objective response was reviewed by an independent committee for 38 first evaluable pts: 1 CR, 17 PR and 12 Stable disease.

Conclusion: Preliminary data suggest that weekly Taxol and Paraplatine is a well tolerated combination with very promising activity in elderly population with NSCLC. Final analysis will be available in September 2003.

803 POSTER

Phase I / II and pharmacokinetic study of Vinflunine (VFL) in combination with cisplatin (CDDP) for treatment of advanced non-small cell lung cancer (NSCLC) in chemonaive patients: Preliminary results.

M. Krzakowski[1], R. Ramlau[2], M. Pinel[3], G. Zorza[3], C. Colin[3], P. Souquet[4]. [1] *The Maria Sklodowska-Curie Memorial Cancer Center, Thoracic Tumours Depertment, Warsaw, Poland;* [2] *Grand Poland Center of Pulmonary Disease abd Tuberculosis, POZNAN, Poland;* [3] *Institut de Recherche Pierre Fabre, Boulogne Billacourt, France;* [4] *Centre Hospitalier Lyon Sud, Pierre Benite, France*

VFL (Javlor®) is a novel semi-synthetic vinca-alkaloid obtained through superacidic chemistry by the selective introduction of two fluorine atoms at the 20'position of vinorelbine (VRL). VFL has shown higher in vivo antitumour activity than VRL in several human tumour models. Platinum-based doublets are the standard of treatment in advanced NSCLC and pre-clinical experiment testing in vitro A549 human NSCLC line has shown synergistic effects of VFL in combination with CDDP. This trial was designed to determine the recommended dose (RD) of the combination (phase I) and, its response rate and safety (phase II) in pts with previously untreated advanced NSCLC. Pharmacokinetic blood sampling was performed to study the absence of mutual interaction VFL-CDDP. Three doses of VFL were investigated 250 mg/m*, 280 mg/m* and 320 mg/m* in combination with CDDP 80 mg/m* once every 3 weeks. Due to the absence of dose limiting toxicities in the first 2 doses of VFL (3 pts per dose), the RD was established at VFL 320 mg/m* plus CDDP 80 mg/m*. Accrual is planned for 40 evaluable pts in phase II (at the RD). As of today, 36 are included and results available for 15 pts with Karnofsky's performance status (KPS) 80 to 100%, measurable disease (WHO) and adequate biological functions. So far, 15 pts (13 males, 2 females; KPS 100%: 5 pts, KPS 90%: 7 pts, KPS 80%: 3 pts; median age: 56 years/range 47-70) are evaluable for response and safety. Five out of these 15 patients achieved partial response (independent radiological review) and, 7 had stable disease. The median number of cycles administered was 5. No grade (G) 3 / 4 anaemia or thrombocytopenia were recorded (NCI-CTC scale), neutropenia G 3 / 4 was seen in 52% of cycles and one episode of febrile neutropenia was reported. Other G 3 non haematological toxicities were: constipation and hiccups 1 episode respectively and abdominal pain 2 episodes. Preliminary pharmacokinetic analysis does not evidence any VFL / CDDP interaction.

Conclusions: VFL / CDDP is a highly active combination in first line treatment of advanced NSCLC, with an excellent tolerance profile; the study accrual is ongoing and updated results will be reported at the meeting. Other combination trials in first line NSCLC have started with carboplatin and gemcitabine.

804 POSTER

Navelbine and Cisplatin with concurrent radiotherapy for unresectable stage III NSCLC

P. Rusu[1], T.E. Ciuleanu[1,2], D. Cernea[1], D. Pelau[1], V. Gaal[1], C. Cebotaru[1], D. Iancu[1], T. Guttman[1], N. Todor[1], N. Ghilezan[1,2]. [1] *Oncology Instinute "Ion Chiricuta", Radiotherapy, Cluj-Napoca, Romania;* [2] *UMF " Iuliu Hatieganu", General Oncology, Cluj-Napoca, Romania*

Purpose: There has been conducted a prospective phase II study to determine the response rate (RR), toxicity and survival (S) of concurrent Navelbine and Cisplatin (2 cycles), with radiotherapy, followed by 2 additional cycles of consolidation chemotherapy with the same drugs, for locally advanced stage III NSCLC. In order to decrease toxicity the role of protectors like amifostine has been evaluated.

Methods and materials: Thirty-three patients with histologically proven NSCLC, unresectable stage IIIA and IIIB, PS=1-2, measurable disease, adequate hematologic, renal and hepatic functions were included the study from 16.11.2000 to 20.11.2002, Patient caracteristics were: median age 59, ranging between 45 - 71, M/F=30/3, PS 1/2=13/20, stage IIIA/IIIB=3/30, squamous cell cc 27, adenocc 2, adenoid chistic cc 1, large cell cc 3. Thetreatment consisted of 2 cycles of chemotherapy with Navelbine (15 mg/sqm, d 1,8, q21) and Cisplatin (80 mg/sqm, d 1, q 21), given concurrently with radiotherapy (60 Gy/30 fractions/ 6 weeks), followed by 2 more cyclesof consolidation chemotherapy with the same drugs (navelbine: 25 mg/sqm d 1,8, cisplatin 100mg/sqm, d1, q 21). Fifteen patients received amifostine (Ethyol WR-272) 740 mg/sqm, d1, 8, q 21, which is an organic thiophosphate, found to have radio and chemoprotective effect. Chemotherapy has been completed by 63% and radiotherapy by 94% patients.

Results: Thirty-three patients were evaluable for toxicity. Grade 3 or 4 neutropenia occurred in 7 patients (21%), esophagitis in 7 patients (21%), digestive toxicities in 4 patients (12%). There was a trend of lower severe toxicities when amifostine was administrated. Of the 31 patients evaluable for response, 4 patients achieved a complete response (CR=13%), 15 patients achieved a partial response (PR= 48%) for an overall response rate (RR) of 61% (confidence interval 44% - 78% at 0.05). Nine patients had stable disease (SD=29%), and 3 patients had progressive disease (PD=10%). As pointed out in the Kaplan Meier's survival curve, the 1-year survival rate was 38%, the median survival (mS) was 11 months, at a median follow up of 9 months.

Conclusions: Preliminary analyses indicate that concurrent Navelbine and Cisplatin (2 cycles) with radiotherapy followed by 2 more cycles of the same drugs given as consolidation chemotherapy for advanced stage III NSCLC is feasible and well tolerated and has a positive effect on the response rate and survival.

805 POSTER

Mitogen-activated protein kinase (MAPK) and Akt as predictive factors for response to ZD 1839 therapy in non-small cell lung cancer (NSCLC) patients

F. Cappuzzo[1], V. Gregorc[2], K. Bencardino[2], L. Lombardo[2], E. Magrini[1], T.C. Paties[2], G.L. Ceresoli[2], S. Bartolini[1], E. Villa[2], L. Crinò[1]. [1] *Bellaria Hospital, Oncology, Bologna, Italy;* [2] *S.Raffaele University Hospital, Radio-Oncology, Milano, Italy*

Background: Predictive factors for response to Tyrosine-Kinase Inhibitors (TKIs) are unknown. ZD 1839 is an oral active, selective Epidermal Growth Factor Receptor (EGFR) TKI, active in 10% of pretreated NSCLC patients. The impressive responses obtained in a so far undefined subgroup of NSCLC patients suggest that, in some patients, the EGFR pathway is crucial for malignant cells survival. EGFR activation leads to cell proliferation via Mitogen-Activated Protein Kinase (MAPK) and blocks apoptosis by phosphorilation of the anti-apoptosis protein (AKT). It is possible that only patients with both MAPK-AKT phosphorilation can benefit from ZD1839 therapy. This trial has been designed to test the hypothesis that clinical benefit (PR+NC lasting at least 6 months) is significantly better in patients with AKT-MAPK activation.

Treatment: Patients with locally advanced or metastatic NSCLC, not suitable for chemotherapy, were treated with ZD 1839 at daily dose of 250 mg until disease progression. At study entry histological specimens were collected, and MAPK/AKT were evaluated by immunohistochemistry.

Patients: Ninety-four patients fulfilled the inclusion criteria and entered onto the trial. Main patient characteristics were: median age 64 years (range 33-83), male/female ratio 59/35, stage IIIA/IIIB/IV 2/14/78, PS 0/1/2 38/46/10. Histology was: 49 adenocarcinoma, 10 bronchiolar-alveolar carcinoma, 19 squamous-cell, 16 undifferentiated. Previous chemotherapy-lines: 0/1/2/3+: 8/39/36/11. Twenty-nine patients were not pretreated with platinum (8 received ZD1839 as first line, 15 after gemcitabine and 6 after gemcitabine and vinorelbine failure). Seventy-five patients were pretreated with platinum and taxanes.

Results: At the time of this analysis only data on clinical activity are available. Response has been evaluated in 78 patients: we observed 12 PR (15.4%), 15 NC lasting at least 6 months (19.2%), 7 NC lasting at least 2 months but less than 6 months (8.9%) and 44 PD (56.5%). MAPK and AKT determination is ongoing

Conclusions: These data confirm the activity of ZD1839 in NSCLC. Data from all 94 patients and evaluation of ZD1839 activity and MAPK-AKT expression will be available for the meeting

806 POSTER

Phase 2 study of first line chemotherapy using CT-2103 (XYOTAX) in patients with non-small-cell lung cancer who are >69 years of age or who have performance status (PS) = 2

D. Bodkin[1], M. Neubauer[2], M.G. Bolton[3]. [1] *Sharp Memorial Hospital, San Diego, USA;* [2] *US Oncology, Dallas, USA;* [3] *Cell Therapeutics, Inc., Seattle, USA*

Background: CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors. CT-2103 exposes normal organs to conjugated paclitaxel, which is non-toxic in vitro, thus minimizing overall toxicity. CT-2103 showed enhanced efficacy compared to paclitaxel/Cremophor in syngeneic and xenogeneic in vivo tumor models including lung tumors. Conjugation of paclitaxel to poly-L-glutamate enhances aqueous solubility and eliminates the need for Cremophor, resulting in a convenient 10-min infusion.

Material and methods: Chemotherapy naive patients with non-small-cell lung cancer (NSCLC) who are >69 years of age or with ECOG PS = 2 are eligible for this open-label, multicenter study. Patients receive a conjugated paclitaxel dose of 175 mg/m2 CT-2103 as a 10-minute IV infusion every 21 days for up to 6 cycles. Safety was assessed using NCI CTC (v 2). Efficacy assessments were done after every second cycle using RECIST.

Results: Twenty-eight patients have been treated. The median age was 76 (range, 49-88). Seven patients (26%) were PS=2; 4 of these were also > 70 years. Of the 25 patients evaluable for response, 18 (72%) achieved disease control; partial response, 2 patients (8%) or stable disease, 16 patients (64%). Fourteen patients (50%) completed 4 or more cycles of therapy. In PS = 2 patients median overall survival (OS) is 5.4 months. In PS = 0 or 1 patients, median OS is 7.8 months. Grade 4 drug-related neuropathy occurred in 2 patients. No other clinically significant drug-related grade 4 adverse events occurred. Grade 3 toxicities were limited to generalized weakness/fatigue (4 patients), neuropathy (3), and febrile neutropenia (1). Neuropathy and weakness/fatigue were seen in patients with concomitant progressive disease and significant disease-related comorbidities.

Conclusions: CT-2103 has demonstrated activity and was well tolerated in elderly and PS = 2 patients with NSCLC. Based on these encouraging results, enrollment in this study will continue with treatment at a higher dose of 235 mg/m2 in patients with PS=2 only. Two randomized phase 3 studies using CT-2103 as a single agent and in combination with carboplatin (Stellar 3 and 4) have been initiated in PS = 2 patients.

807 POSTER

Phase I trial of Cisplatin, Etoposide and CPT-11 triplet in patients with advanced stage SCLC. A Hellenic Cooperative Oncology Group study.

E. Briasoulis[1], E. Samantas[2], H. Kalofonos[3], D. Skarlos[4], C. Christodoulou[4], G. Fountzilas[5], A. Bamias[6], M.A. Dimopoulos[6], P. Kosmidis[7], N. Pavlidis[1]. [1] *University of Ioannina, Medical School, Oncology Dept, Ioannina, Greece;* [2] *Agioi Anargyroi Cancer Hospital, Athens, Greece;* [3] *University of Patras, Med. Oncology Sect., Patra, Greece;* [4] *Er. Dynan Hopsital, 2nd Med. Oncology Dept, Athens, Greece;* [5] *University of Thessaloniki, AHEPA Hospital, Oncology Sect., Thessaloniki, Greece;* [6] *University of Athens, Alexandra Hopsital, Athens, Greece;* [7] *Ygeia Hospital, Med. Oncology Dept, Athens, Greece*

Background: The unsatisfactory survival figures of extensive stage SCLC prompted us to develop a novel triplet by combining CPT-11, a most promising camptothecin derivative with the Etoposide-Cisplatin doublet which is considered standard therapeutic regimen for this type of cancer. This trial aimed to investigate the feasibility and toxicity and to define the optimal recommended dose (ORD) for phase II evaluation of the study regimen (CEC). Reporting of antitumor activity was a secondary endpoint.

Material and Methods. This was a multicenter dose finding study of single shot CPT-11 combined with cisplatin 20 mg/m^2 plus etoposide 75 mg/m^2 both given intravenously for 3 days. Eligible patients had advanced stage SCLC and normal liver and kidney functions. CPT-11 was escalated by steps of 40 mg/m^2 staring from 60 mg/m^2. Maximum Tolerated Dose (MTD) was defined the dose level where 2/6 patients at minimum developed dose limiting toxicity (DLT). The Common Toxicity Criteria v2 were used for toxicity assessment and the RECIST criteria for response evaluation. By design, at least 12 patients should be treated at mid-step between the MTD and the previous dose level, randomised to receive CPT-11 on day1 or day3 to better define the ORD and timing for CPT-11 administration.

Results. From March 2001 to December 2002, 37 registered patients received 199 treatment courses (median per patient cycles 6) at 4 dose levels of CPT-11: 60 mg/m2 (7 pts), 100 (5 pts), 140 (9 pts) and 120 (16 pts). Demographics: 35 male, median PS 1 and age 66. The MTD for this regimen was achieved at CPT-11 dose 140 mg/m^2. At the MTD 4/6 patients experienced DLT: 3 pts developed febrile neutropenia and one patient grade 3 diarrhea. Median time to nadir neutrophil counts was day 16 (range 13-19). The ORD was 120 mg/m^2 for CPT-11 combined with 20 mg/m^2 Cisplatin and 75 mg/m^2 Etoposide over 3 days and recycled every 3 weeks. Toxicity at ORD was acceptable: 3/16 cases had short-lived neutropenia and 3/16 diarrhea grade 2-3. There was no difference in toxicity between the two time-schedules of CPT-11 administration. Other toxicities reported were mild asthenia, vomiting and neurotoxicity. Among 30 evaluable for response patients a 73% objective response rate was documented with complete response observed in 5/6 cases with brain metastases. Median duration of response was 8 months.