hematological or non-hematological toxicities. Only 1 patient had grade 3 thrombopenia; grade 3 anemia or neutropenia were not observed. Severe non hematological toxicity also was uncommon: grade 1-2 fatigue/asthenia in 27 patients (61%); grade 1-2 motor neuropathy in 26 (59%) and grade III in 4 (9%); grade 1-2 sensory neuropathy in 25 patients (57%); alopecia was mild.

Conclusion: Low-dose weekly paclitaxel regimen has good clinical efficacy with low toxicity in previously treated patients with advanced NSCLC, and may provide an additional treatment option for these population.

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A phase I/II study of weekly irinotecan combined with weekly cisplatin in patients with advanced non-small cell lung cancer

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Purpose: Synergistic effects between irinotecan and cisplatin have been reported. We had conducted a phase I trial combining these agents to determine the maximum-tolerated dose of weekly irinotecan plus weekly 20 mg/m2 cisplatin. Following a phase I study, we have conducted a phase II study to confirm the efficacy and safety of this combination therapy. Methods: For a phase I study, patients with advanced solid tumor, aged ≤ 75 years, performance status ≤ 2, and adequate organ functions were enrolled. They were treated at 4-week intervals using each dose of irinotecan plus fixed dose (20 mg/m2) of cisplatin on days 1, 8, and 15. The starting dose of irinotecan was 40 mg/m2 (level 1), and escalated in 10 mg/m2 increments until the maximum dose of 90 mg/m2 (level 6). In addition to severe toxicities, inability to complete the full-dose chemotherapy was considered as a dose limiting toxicity. After determining the recommended dose, a phase II study was conducted to previously untreated patients with non-small cell lung cancer (NSCLC). Results: In level 6 of a phase I study, dose limiting toxicities were observed in 3 of 9 patients (two for severe toxicities and one for inability to complete the initial two courses). Although the dose of irinotecan did not reach to the maximum-tolerated dose, the dose of irinotecan for the following phase II study was determined 90 mg/m2 according to the study design. For a phase II study, final goal is 100 patients. So far, 32 patients with advanced NSCLC were evaluated. All were assessable for toxicity and response. Response rates of NSCLC was 46% (13/32). Median response durations of NSCLC was 80 days. Total number of cycles administered was 95, and median number of cycles of NSCLC was 3. In 68 of 95 cycles (71.6%), anti-cancer agents were administered without skip. Dose reduction was performed in 25 cycles of 95 cycles. Toxicities were generally mild and reversible; toxicities over grade 3 were as follows; neutropenia (34.4%, 11/32), anemia (21.9%, 7/32), thrombocytopenia (3.1%, 1/32), diarrhea (25%, 8/32), anorexia (28.1%, 9/32), nausea and vomiting (18.8%, 6/32), abdominal pain (3.1%, 1/32). Conclusion: The recommended dose of irinotecan is 90 mg/m2 in the present study. The combination of weekly irinotecan and weekly cisplatin seems to be active against lung cancer

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The sequential administration of cisplatin-etoposide followed by topotecan in patients with extensive stage small cell lung cancer (SCLC). A multicenter phase II study

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We studied the sequential administration of topotecan after cisplatin-etoposide in patients with extensive stage SCLC.

Patients and Treatment: 38 patients with previously untreated extensive stage SCLC received 4 cycles of cisplatin 75 mg/m^2 IV on day 1 and etoposide 100 mg/m^2 IV on days 1–3 every 21 days followed by 4 cycles of topotecan 1.5 mg/m^2 IV on days 1–5 every 21 days. The median age was 63 and the performance status (WHO) was 0, 1 and 2 in 5, 25 and 8 patients, respectively.

Results: All patients were evaluable for toxicity and 32 for response. Overall 5 (16%) patients achieved CR and 15 (47%) PR for an overall response rate of 63% (95% c.i. 45.7–79.2). Among 19 patients achieving PR with cisplatin-etoposide, 4 (21%) achieved CR with topotecan. After a median follow up of 8 months, the median duration of response was 5 months, the time to tumor progression was 6.5 months and the probability of one-year survival was 37%. A total of 136 cycles of cisplatin-etoposide and 89 cycles of topotecan have been administered with a median number of cycles per patient 4 for each regimen. There were 2 toxic deaths after cisplatin-etoposide associated with grade IV febrile neutropenia. Treatment delays due to toxicity occurred in 17 cycles of cisplatin-etoposide and 20 cycles of topotecan while doses were reduced in 7 and 4 cycles, respectively. The incidence of grade 3–4 neutropenia, thrombocytopenia and febrile neutropenia was 24.5%, 2% and 3% after cisplatin-etoposide and 21%, 11% and 1% after topotecan. Non-hematologic toxicity was mild. The delivered dose intensity was 100% for cisplatin and etoposide and 82.5% for topotecan.

Conclusions: The sequential administration of cisplatin-etoposide followed by topotecan is a feasible and effective regimen in extensive stage SCLC.

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Chemotherapy with gemcitabine in elderly patients (or in patients not candidate for a cisplatin regimen) with advanced NSCLC: a multicenter phase II study

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Rationale: In a previous study we demonstrated in elderly patients with advanced NSCLC and in pts not candidate for a cisplatin regimen due to concomitant diseases or poor performance status that Gemcitabine administered at the dose of 1000 mg/sqm iv days. 1,8,15 every 28 is active and well tolerated (S.Ricci, Lung Cancer 2000). To improve the dose intensity of Gemcitabine and the compliance to the treatment we have performed a multicenter phase II study with the following schedule: Gemcitabine 1500 mg/sqm iv days 1,8 every 21 for 4 courses. The pts. with SD or OR after 4 courses of chemotherapy were randomized to receive futher 4 cycles of manteinance chemotherapy with Gemcitabine 1200 mg/mq iv days. 1,8 every 21 or best supportive care in order to evaluate the impact on TTP and OS. Patients characteristics: 110 patients were enrolled, 98 males and 12 females; median age 75 yrs range (50-84). PS: 0 = 42, 1 = 44, 2 = 22, 3 = 2; 30 pts. were adenocarcinoma., 53 squamous, 27 NSCLC.

Total number of cycles administered was 270 (median 4 cycles); we observed the following hematological and not hematological toxicity

	G1	G2	G3	G4
Neutropenia	0,7	2,6	0,7	–
Nausea/Vomiting	18,9	7,8	–	–
Thrombocytopenia	3,0	–	0,4	–
Diarrhoea	2,2	0,4	–	–
Anemia	15,6	3,0	0,7	–
Stomatitis	1,1	2,2	–	–
Skin Toxicity	1,1	–	–	–
Fever	8,9	2,2	–	–

Responses: up to now 88 patients are evaluable for response: 12 (13,6%) PR, 23 (26,1%) SID, 53 (60,2%) PD.

Conclusions: The Gemcitabine administered at the dose of 1500 mg/sqm iv days. 1,8 every 21 is active and well tolerated with a good compliance in elderly pts or in pts not candidate for a cisplatin regimen. The study is ongoing in order to evaluate the role of maintenance therapy.

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ZD0473 phase II monotherapy trial in second-line non-small cell lung cancer

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Aims: ZD0473 (cis-amminedichloro[2-methylpyridine]platinum [II]) is a new generation platinum drug designed to have an extended spectrum of antitumor activity and overcome platinum resistance mechanisms. A Phase II open-label, multicenter trial, was designed to assess the efficacy and tolerability of ZD0473 in patients with non-small cell lung cancer (NSCLC) who have failed previous platinum-based therapy.

Methods: Patients received 120 mg/m2 1-hour iv infusion of ZD0473 on day 1 every 3 weeks (with the option of escalating to 150 mg/m2 if the starting dose was well tolerated). Subsequently, the starting dose was modified to 150 mg/m2 following a safety review, showing that 120 mg/m2 was well tolerated. Patients were evaluated in 2 cohorts: drug resistant (relapsed/progressed ≃12 weeks following completion of first-line platinum therapy) or drug sensitive (relapsed/progressed >12 weeks).

Results: To date, 45 patients have been recruited to this study (29 resistant, 16 sensitive; 23 female/22 male; median age 59 years [range 38-77 years]; 39 with performance status 0/1). Eighteen patients received a starting dose of 120 mg/m2 (9 of whom were then escalated to a dose of ~150 mg/m2), while 27 patients received a starting dose of 150 mg/m2. A total of 116 cycles of treatment were delivered (median 2, range 1-9). Most patients did not require dose reductions or delays (34/45). Hematologic toxicities rated as grade 3/4 included: thrombocytopenia (21 patients), neutropenia (11) and anemia (6). The most commonly reported grade 3/4 non-hematologic observations were: lethargy (7), dyspnea (7) and pneumonia (6), irrespective of causality. There were 6 withdrawals due to adverse events, 3 of which were drug related. No drug-related deaths occurred. Disease stabilized in 13/34 evaluable patients (6/20 resistant and 7/14 sensitive), 3 of whom showed some evidence of tumor shrinkage. Twenty-four patients were still alive at this interim analysis.

Conclusion: ZD0473 has a manageable safety profile. Antitumor activity has been seen in terms of disease control. Currently, the data are not mature enough to assess time to progression. The trial is ongoing.

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Oral ZD1839 (iressa) in non-small cell lung cancer (NSCLC): preliminary results from a series of patients at the Istituto Clinico Humanitas, Rozzano-Milano

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Background: ZD1839 (Iressa) is an orally active, selective EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) which blocks signal transduction pathways implicated in cancer growth. Phase I studies showed ZD1839 to be well tolerated (principal adverse events were mild diarrhoea and skin rash) with evidence of activity most notably in NSCLC patients.

Aim: We aimed to assess the anti-tumour activity and tolerability of ZD1839 in a series of patients with previously treated, advanced NSCLC. ZD1839 was provided on a named-patient basis.

Results: So far, we have treated 24 patients (20 male) at our Institute with oral ZD1839 (250 mg). The majority of our patients (n=23) had received prior cisplatin-based therapy, with 14 patients having received 2 prior regimens, and 9 having received 1 prior regimen. One patient had received no previous treatment due to medical contraindications. We have evaluated the efficacy and tolerability of ZD1839 in 20 of these patients. Of the remaining 4 patients, one was withdrawn from treatment during week 1 due to disease progression and 3 are too early for assessment. One patient has had a partial reponse which has lasted for over 3 months and two additional patients have had partial responses each for over a month. Furthermore, one patient has had a minor response. The EGFR status of these pts is being evaluated. In general, ZD1839 was well tolerated; the most frequent adverse event which we observed was grade 1/2 acneiform skin rash which was seen in 11 patients.

Conclusion: These anecdotal results indicate that ZD1839 has promising activity and is well tolerated in patients with advanced, previously treated NSCLC.

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Biweekly gemcitabine in two hours infusion combined with cisplatin for advanced non-small cell lung cancer (NSCLC): preliminary results of a phase II trial

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Introduction: The combination of Cisplatin (C) and Gemcitabine (G) in one of the accepted standards in the treatment of the advanced non-small cell lung cancer (NSCLC), and one of the most used in Europe The habitual guideline of administration of G is days 1+8, which sometimes creates problems of hematologic toxicity, specially in form of trombocitopenia. For that reason, we designed a phase II study to explore the activity and toxicity of the administration of biweekly G in 2 hours combined with C

Material and Methods: C, 100 mg/m2 day 1 and G, 1,500 mg/m2 in infusion of 2 hours, days 1 and 15, in cycles every 28 days, were delivered. Criteria of selection: stages IIIA, IIIB or IV; PS 0-2; measurable disease; absence of previous treatment of disseminated disease; suitable renal, liver and bone marrow functions; absence of cerebral mts. in the diagnosis; informed consent. Calculated sample size: 46 pts.

Results: 43 pts. have been included, 40 male (93%), 3 female (7%). Median age: 59 años (37-72). ECOG: 0: 2 (4.6%); 1: 32 (74%); 2: 9 (21%). Histology: Epidermoid: 28 (65%); AdenoCa.; 13 (30%); Indiferenciated: 2 (4.6%). Stages: IIIA: 4 (9.2%); IIIB: 23 (53%); IV: 16 (37%). Treatment: 165 courses were delivered (mean: 4), Delays in 28 courses (17%) and reductions in 45 (27%). Dose intensity of C: 93%; of G: 85%. 12 pts. received RT, 1 surgery and 16 received 2nd line CT. Response: 38 pts. were evaluable. CR: 4 (10.5%); PR 14 (37%); SD (R minor + stabilizations): 15 (39,4%); P: 5 (13%); CR + PR: 47,5%. Time to progression: 6,7 months. Toxicity (G 3-4): Anemia: 9 courses (5,4%); Neutropenia: 17 courses (10.3%); Trombocytopenia: 1 course (0,6%); Non-haematological: 20 (12%). There were no febrile neutropenia episodes nor toxic deaths. Survival: 38 pts. were evaluable. Mean: 10.1 months; Survival 1 year: 37,5%; survival 2 years: 6,2%.

Conclusions: Combination of C + G delivered on days 1+15 allows a high dose intensity with very low toxicity. Efficacy and survival of this combination is comparable to those obtained with far more toxic schemes.

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A three-week schedule of gemcitabine plus cisplatin as induction chemotherapy for stage III non-small cell lung cancer (NSCLC): final results of a monoinstitutional phase II study

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Background: Gemcitabine-cisplatin combination is an active regimen in the actual 'standard' therapy of advanced NSCLC. Aim of this monoistitutional phase II study was to evaluate the activity of a three-week schedule of this regimen as induction chemotherapy in unresectable stage III NSCLC.

Design: From October'97 to July '00, seventy consecutive, not selected untreated patients (pts), staged with FBS, body CT scan and mediastinal surgical techniques, were enrolled in this study and received gemcitabine 1250 mg/m2 on days 1, 8 and cisplatin 70 mg/m2 on day 2, every 21 days far a median of 3 cycles (range 1-6).

Patients: Demografy was: M/F 56/14; median age = 64 (range 43-75); PS 0/1/2 = 20/34/16; histology: squamous/adenocarcinoma/large-cell = 37/22/11; stage IIIA/IIIB = 47/23

Results:69 pts were evaluable for response and toxicity; 1 patient early dropped out after first dose of G. Three pts (4.2%) achieved a CR, 37 pts (52.8%) obtained a PR, 25 pts (37.5%) a SD and only 4 pts (5.7%) progressed (3 IIIB and 1 IIIA). The intention-to-treat overall RR was 57% with a RR of 68% in stage IIIA disease and 34.7% in stage IIIB. Of 40 responsive pts 30 underwent thorachotomy and 28 (40%) were completely resected; among these 23 were at stage IIIA and 5 at stage IIIB. A pathological complete response was found in 2 pts and pathologic tumor downstaging was obtained in 16 pts (25.7%). Forty-eight pts received RT (Gy 54-65) after induction chemotherapy; among these 31 had clinical evidence of disease and 12 (38.7%) obtained a further RR. By October '99, 39 out pts 70 have died and 56 are evaluable for 1-year survival. The median follow-up was 16 months. The median survival time was 14.5 months, whereas 1-year survival probability was 67%.

Haematological toxicity was mild: WHO grade 3-4 neutropenia and thrombocytopenia occurred respectively in 21.7% and 26% of pts; febrile neutropenia was observed in 2.9% of cases without toxic deaths. WHO grade 1-2 dysphagia occurred in 5/49 pts (10%) of irradiated pts without pulmonary toxicity. Others non-haematological toxicities were mild.

Conclusions: This phase II study confirm that gemcitabine-cisplatin is a very active and safe induction regimen in stage III desease, even with a three-week schedule in addition to favorable results obtained with 28 days schedule. Future investigations will explane the role af a three drugs combination as induction therapy for stage III NSCLC.