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.