included in the study. If less than 4 responses occurred in the first 19 registered patients, the study should be closed. Otherwise, accrual had to be pursue until a minimum of 55 eligible patients.

Results: 64 eligible patients were registered between 08/1998 and 01/2003. At this time, 56 patients have been evaluated. Their principal characteristics were: median age 62 years (41-78), median Karnofsky performance status 90, stage I/II/III/IV 23/1/12/20, histological type (epitheliomatous/sarcomatoïd/mixed) 33/9/3, male/female 48/8. Among 51 assessable patients, we observed 6 partial responses after 3 cycles. The best overall response rate at 6 cycles was 17.6% (9 PR) (IC 95% 7.1%-28.1%). After 3 cycles, grade III/IV leucopenia and thrombopenia were respectively observed in 48.1% and 0% of the patients. Non haematological toxicity was mild with grade II/III nausea and vomiting in 50% of the patients.

Conclusions The preliminary results of our phase II trial demonstrate the potential activity of the combination of cisplatin and epirubicin in malignant mesothelioma, with an objective response rate of 17.6%. Except for leucopenia, this regimen is well supported and compares adequately with other active combinations

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A randomized phase II trial of gemcitabine and either day 1 or day 8 carboplatin for advanced non-small cell lung cancer (NSCLC)

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Background: Chemotherapy with platinum-containing regimens has been found to produce an improvement in survival and quality of life in patients with advanced NSCLC. The primary objectives of this study were to determine the toxicity and efficacy of gemcitabine (days 1 *and* 8) and carboplatin (on either day 1 *or* 8; Carb d1 or Carb d8 arms) in patients with advanced NSCLC. Secondary objectives included quality of life, duration of response, time to disease progression and survival.

Methods: This was a multi-center, open-label, randomized Phase II study. Eligible patients had histologically or cytologically proven Stage IIIB or IV NSCLC, with ECOG performance status $\leq$ 2. Gemcitabine (1000 mg/m^2) was given as an intravenous infusion over 30 minutes on days 1 and 8 of a 21-day cycle with carboplatin (AUC 5) given as a 1-hour infusion immediately after the gemcitabine infusion on day 1 or day 8.

Results: Forty patients were enrolled in this study, with 20 patients (pts) in each arm (mean age 62 yr; 17 females, 23 males; 9 pts with Stage IIIB disease, 31 pts with Stage IV disease). Reasons for treatment discontinuation were: therapy completed according to protocol (8 cycles) (7 pts), death due to study disease (2 pts), adverse event (1 pt), lack of efficacy/progressive disease (14 pts), patient decision (1 pt), physician decision (14 pts) and protocol violation (1 pt). There were 4 partial responses in the Carb d1 arm and 6 partial responses in the Carb d8 arm, giving an overall response rate of 25%. There were no statistically significant differences between the two arms for median survival time (40.7 weeks in the Carb d1 arm, 39.1 weeks in the Carb d8 arm), time to progression (28 weeks Carb d1, 29.5 weeks Carb d8), or time to treatment failure (14.6 weeks Carb d1, 17.1 weeks Carb d8), and the one-year survival results were similar (27.8% Carb d1, 33.3% Carb d8). The achieved dose intensities of both gemcitabine and carboplatin were significantly higher in the group that received carboplatin on day 1 than in the day 8 group. Toxicities of note included grade 3/4 neutropenia (15 pts Carb d1, 11 pts Carb d8); grade 3/4 thrombocytopenia (14 pts Carb d1, 7 pts Carb d8); grade 3/4 dyspnea (5 pts Carb d1, 3 pts Carb d8); and febrile neutropenia (1 pt Carb d1). Nine patients in the Carb d1 arm, but only one patient in the Carb d8 arm, required a platelet transfusion. There was no clear difference in quality of life, as assessed by the EORTC QLQ-C30 and QLQ-C13 scales after three and six cycles of treatment.

Conclusion: The two gemcitabine-carboplatin schedules were of similar, moderate efficacy in treating patients with advanced NSCLC, however, fewer patients in the arm that received carboplatin on day 8 experienced grade 3/4 neutropenia and thrombocytopenia and required platelet transfusions.

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CPT-11- Gemcitabine as second line chemotherapy in small cell lung cancer (SCLC). A multicentric phase II trial.

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Background: CPT-11 and Gemcitabine have shown activity in SCLC even in pretreated patients (pts). We conducted a prospective phase II study to determine the activity of this combination as second line treatment in pts with SCLC.

Patients and methods: Pts were eligible if they had measurable or evaluable disease, performance status (ECOG) 0-2 and adequate hepatic, renal and bone marrow function. CPT-11 dose was 150 mg/m^2 (90-minute IV infusion) day 1, and Gemcitabine dose was 1500 mg/m^2 (30-minute IV infusion) day 1. Cycles were administered every 2 weeks.

Results: 47 pts were enrolled, 38 male and 9 female. Median age was 64 years (range 42- 78); 91.5% had PS 0 or 1. Twenty-seven pts had sensitive disease and twenty refractory disease (defined as progression within 3 months of starting first-line treatment). A total of 306 courses have been administered (median 6 per patient, range 1 -12).

To date all the pts were evaluable for toxicity and 39 for efficacy. Response rate (RR) was 31% (95% C.I: 17 47.6%), 1 patient with sensitive disease achieved a complete response (2.5%). 33% of pts showed stable disease (SD) and 36% progression (PD). The RR in refractory disease was 22.2%(95% C.I: 6.4 47.7%), SD 38.9% and PD 38.9%. In sensitive disease RR was 38% (95 C.I: 18 61.6%), SD 28.6% and PD 33.3%. Median duration of response was 3 months, median time to progression 6 months (95% C.I: 4.5 7.4 m) and median survival 9.3 months (95% C.I: 5.8 12.8 m).

Toxicity was very mild without grade 3- 4 hematological toxicity. Non-hematological toxicity was also mild, grade 3-4 toxicity including was observed in <1% of cycles (Nausea/ vomiting, asthenia, renal, hepatic or diarrhea). 3 pts developed skin toxicity grade 1-2, and 5 alopecia grade 1 3.

Conclusions: This combination is active as second line treatment of SCLC, showing an encouraging median survival. The profile of toxicity is very mild. Further development of this combination is warranted.

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New EGFR variants around the EGFRvIII region in non-small cell lung cancers(NSCLC)

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Epidermal growth factor receptor (EGFR) is a 170kDa transmembrane glycoprotein and is overexpressed in various human malignancies including NSCLC. While it is a potential target for prevention and therapy, EGFR is also expressed by normal lung. An RNA variant (EGFRvIII) has been described in a number of tumors including NSCLC in which there is an 801bp deletion (exon 2 to 7). This variant has been reported in tumors but has been absent from normal lungs and cell lines. Its absence from normal lung suggests that it may be used as a biomarker or chemotherapeutic target. However, there are few clinical reports on EGFRvIII in lung cancers to date. One immunohistochemical study has found EGFRvIII in 16% of non-small cell lung cancers. While EGFRvIII has been detected by RT-PCR and sequenced in gliomas, prostate cancers, and breast cancers, no similar studies have been carried out in lung cancers so far.

We examined total RNAs from 18 NSCLC cell lines, 6 benign bronchioepithelial primary culture cells, and 48 non-small cell primary lung tumors by RT-PCR (regular RT-PCR or nested RT-PCR) using several primer pairs spanning EGFRvIII (EGFR exon 1-8). When a truncated EGFR variant was present in PCR reaction mixture, we isolated the truncated product from ethidium bromide stained agarose gels and sequenced the cDNA created from the isolated product.

We were unable to confirm the presence of EGFRvIII in NSCLC cell lines, primary tumors, or normal bronchioepithelial primary culture cells. Wild type EGFR was demonstrated in 78% primary tumors, 94% cell lines, and 83% bronchioepithelial primary culture cells. In addition, we found 10 truncated EGFR variants that did not correspond by sequence analysis to EGFRvIII. These new variants were present at variable copy number. They may not be