We have determined telomerase activity and p16 expression in a series of 98 prospectively collected non-small cell lung tumours obtained from patients who had suffered only surgery. Telomerase activity was investigated by a TRAP-ELISA based procedure, and p16 expression by Western-blot followed by promoter hypermethylation analysis in cases showing lack of p16 expression. Associations with survival were evaluated.

Positive results for telomerase activity were found in 82% of the cases, this variable being correlated with poor differentiation and recurrence of tumours. Lack of p16 expression was observed in 61% of tumours, 36% of which showed promoter hypermethylation. By univariate analysis, both negative telomerase activity and p16 positive expression were significantly correlated with a better prognosis of patients. Moreover, statistics for equality of survival distributions for telomerase, adjusted for p16, resulted significant by Breslow test (P = 0.03). These results indicated a positive interaction between the two parameters evaluated in this work, telomerase activity and p16 expression. For telomerase positive tumours, p16 expression emerged as a significant protective variable, independent of tumour stage, as indicated by Cox multivariate analysis (Relative Risk, RR = 0.214; P = 0.014).

These results suggest that the combined telomerase activity and p16 expression analyses may be considered of prognostic importance in non-small cell lung cancer.

165 POSTER

A randomized phase III trial of docetaxel (D) and cisplatin (P) versus vindesine (V) and p in stage IV non small cell lung cancer (NSCLC)

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Purpose: The purposes of this randomized study were to compare the survival, anti-tumor response and tolerability between DP and VP, Japanese standard regimen as of 1998, in patients with untreated stage IV NSCLC.

Methods: Eligible patients (pts) had measurable disease, adequate organ function and ECOG PS 0-2. Pts with PS 3 due to pain from bone metastasis or pts with asymptomatic brain metastasis were included in this study. DP consisted of P 80mg/m2 (day 1) and D 60mg/m2 (day 1), repeated every 3-4 weeks. No prophylactic steroid for edema was administered. VP consist of P 80mg/m2 (day 1) and V 3mg/m2 (day 1, 8, 15), repeated every 4 weeks. Crossover administration of D and V was prohibited for both treatment groups.

Results: Among 311 pts enrolled from 4/98 to 3/00 of whom 302 pts were assessable. 151 pts received DP and 151 pts received VP. Patient characteristics were; [DP arm] median age 63(30-74), median PS 1(0-3), histology (Adeno/Squamous/Other) 120/17/14, male/female 97/54, median delivered cycles 3(1-9), [VP arm] median age 64(39-74), median PS 1(0-3), histology (Adeno/Squamous/Other) 103/33/15, male/female 103/48, median delivered cycles 2(1-5).

Median survival times (MST) were 11.3 months vs. 9.6 months and 1-year survival rates were 48% vs. 43% for DP arm and VP arm, respectively. Response rate (RR) were 37% (56/151) for DP arm and 21% (32/151) for VP arm ($p<0.01$). Toxicity was assessed by NCI-CTC scale. Severe hematological toxicities were developed with similar profiles. (Grade 3-4 toxicity, DP arm; leukopenia 46%, neutropenia 75%, thrombocytopenia 1%: VP arm; leukopenia 68%, neutropenia 78%, thrombocytopenia 0%). On severe (grade3-4) non-hematological toxicity, diarrhea was observed higher in DP arm (9% vs. 1% $P<0.01$). Severe edema was not observed and other severe toxicities were rare in both arms.

Conclusion: Although both regimens were well tolerated, DP arm shows a significantly higher RR and shows better MST and 1-year survival rate than VP arm. DP combination chemotherapy should make one of the new standard regimens against NSCLC. Updated data will be presented at the meeting. Supported by Aventis Pharma Japan.

166 POSTER

Early prediction of response in patients with NSCLC stage III and IV during platin based chemotherapy by FDG-PET

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Rationale: This study was done to detect early after one cycle of platin based chemotherapy patients responding or not responding to chemotherapy.

Patients and Methods: 29 patients (6 f, 23 m, age: 61 ± 8 years) with histopathologically proven NSCLC stage III and IV underwent 2 to 8 cycles of platin based chemotherapy. A dynamic FDG-PET (injection of 300–400 MBq F-18-FDG) was performed prior to and three weeks after one cycle of chemotherapy (CTX). The chemotherapy used was cisplatin/vinorelbine (10), carboplatin/taxol (15), cisplatin/taxotere (3) and cisplatin/etoposide (1). Quantitative measurements of tumor FDG uptake were correlated with radiologically response after 2 cycles CTX measured with CT scan in accordance to WHO criteria. FDG uptake was quantitatively assessed by standardized uptake values (SUV, measured 40–60 min p.i.).

Results: Radiological response was 0/30 complete response, 11/30 partial responses, 10/30 stable diseases and 8 progressive diseases after 2 cycles of CTX. There was no significant correlation between the absolute FDG-uptake prior to CTX or after 1 cycle of CTX with the later response. But there was a significant correlation between the decrease of SUV and subsequent response ($p < 0.0001$) using a cut-off value of 18% reduction of FDG uptake. In responders FDG uptake decreased by 44% ± 15% while in non-responders the decrease was only 7% ± 21%. Response was predicted with a sensitivity of 100% and a specificity of 89%.

Conclusion: With FDG-PET a later response to CTX can be predicted very early with a high accuracy. The early detection of useless CTX can save side effects in non-responding patients. Furthermore the CTX can be modified early to a possible effective CTX to preserve the patients quality of life.

167 POSTER

A phase II study of LY355703 (cryptophycine) as first-line therapy for stage IIIb or IV NSCLC subjects: preliminary analysis

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Introduction: LY355703 (Cryptophycine-52) is a synthetic analogue derived from blue-green algae that inhibits microtubule dynamics. In phase I studies, one patient with NSCLC previously treated with taxanes achieved a PR lasting 4 months.

Purpose: The primary objective was to determine the objective response rate (CR or PR) The secondary objectives were 1) characterize the nature of toxicity; 2) measure time-to-event efficacy variables; and 3) characterize pharmacokinetics and identify potential factors that may influence LY355703 disposition in cancer subjects.

Patients & Methods: The trial involved two stages, with 18 patients enrolled in first stage. If at least 2 subjects responded to LY355703 therapy another 22 patients would be enrolled into the second stage. Since May 2000, 14 patients (12 male, 2 female with a median age of 58 yrs, range 41 - 70 yrs, all stage IV and WHO Performance Status of 0 or 1) received LY355703 1,5 mg/m2 iv over 2 h on days 1 and 8 of a 21-day-cycle following prophylactic hypersensitivity therapy. Two patients are currently ongoing in the study and are not included in this abstract.

Results: Fourteen patients received a total of 24 cycles; of these, 7 patients received 1 cycle, 5(2), 1(3), 1(4). No objective tumor responses were observed. Reasons for discontinuation included lack of efficacy (9 patients) and adverse events (3 Patients). Two patients died on study. One was hospitalized for Grade 4 diarrhoea and died from severe lactat acidosis possibly related to LY355703. The other patient suffered a myocardial infarction and died. Haematological toxicities were not observed. Other toxicities experienced were alopecia, constipation, fatigue, myalgia, arthralgia, neuropathy, tumor pain and hypertension. Two patients had acute hypersensitivity reactions (Grade 2) despite prophylaxis.

Conclusions: The trial has been suspended pending the result of the 2 ongoing patients and other ongoing phase II LY355703 trials. Supported by grant from Eli Lilly and Company.