P3-098 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Multicenter, randomized phase II trial of CI-1033, an irreversible pan- erbB inhibitor, for previously treated advanced non-small cell lung cancer

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Purpose: To evaluate the efficacy of the pan-erbB inhibitor, CI-1033, in platinum-refractory or recurrent advanced stage non-small cell lung cancer.

Patients and Methods: This open label randomized phase II trial evaluated CI-1033 in patients with advanced stage NSCLC who failed or were refractory to platinum-based chemotherapy. Three oral CI-1033 doses were evaluated in 21-day dosing cycles - 50 mg daily for 21 consecutive days; 150 mg daily for 21 consecutive days; and 450 mg daily for 14 consecutive days followed by 7 days of no treatment. The primary efficacy endpoint was the 1-year survival rate.

Results: One hundred sixty six patients were randomized. Baseline patient demographics were well balanced. The most common drug related adverse events were rash and diarrhea. The 450 mg arm (14 days on/7 days off) was closed early due to an excessive rate of adverse events. The 1-year survival rates were 29%, 26% and 29%, respectively in the 3 arms. The response rates were 2%, 2% and 4% and stable disease was confirmed in 16, 23% and 18% of patients, respectively in the 3 study arms. Exploratory analyses demonstrated a prolonged survival in patients who developed a rash and in those with baseline tumor ErbB-2 expression.

Conclusions: CI-1033 had modest activity in unselected NSCLC patients but did not meet its primary endpoint. Future studies should focus on identifying methods of patient selection.

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EGFR expression in 369 patients surgically treated for non small cell lung carcinoma; correlation between gene copy number and protein expression

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Background: Lung cancer is one of the most frequently occurring neoplastic disorders and overall survival is less than 15%. To identify patients with advanced non-small cell lung cancer (NSCLC) likely to benefit from treatment with anti-EGFR tyrosine kinase inhibitors, EGFR gene copy number determined by fluorescence in situ hybridising (FISH) and EGFR protein determined by immunohistochemistry (IHC) has been used. However, the results have been conflicting, and as most published studies contains few patients and it is difficult to get enough tumour tissue from patients with advanced NSCLC to construct high throughput tissue micro arrays (TMA), we studied 369 patients surgically treated for NSCLC at the University Hospital of Lund during the time periods 1981-83 and 1995-97. There were 151 squamous cell carcinomas, 120 adenocarcinomas, 44 large cell carcinomas, 10 small cell carcinomas, 26 carcinoids and 18 other tumours. Materials and methods: A TMA with three cores from each case was constructed and evaluated for EGFR protein expression by IHC and FISH for gene copy number. IHC was evaluable for 340 cases. It was scored 0-3+ using virtual microscopy with an Aperio Scanscope. Score 0-1+ were considered as negative and 2-3+ as positive. Also, 342 cases were evaluable for gene copy number by FISH and scored as negative; non amplified (NA), and positive; polysomy (usually 4-12 copies of both the EGFR gene and chromosome 7) and amplified.

Results: IHC; 0+ = 136, 1+ = 64, 2+ = 67, 3+ = 73. All cores containing viable tumour tissue could be evaluated. Also, hybridizing was successful with all cores containing viable tumour tissue; NA = 202 (a few cases with trisomy was scored as NA), polysomy = 117, amplified = 23. Of the cases, 321 pairs were evaluable for both tests and the correlation between IHC and FISH was highly significant (Wilcoxon, p = 0.000000). Survival; In the cohort treated in 1995-97 the overall one year survival vas 87%, three year survival 66% and five year survival 58%. Of those that survived less than one year, 16/23 (70%) were positive with FISH compared to 62/149 (42%) of the others (p = 0.012). For three and five year survival no significance were reached either for FISH or IHC. When data from the 1981-83 cohort was added the overall 5 year survival was 50 %. Detailed survival data from the whole cohort are in progress! What´s new? This is one of the largest studies of EGFR gene copy number in NSCLC. It is also, to our knowledge, the first study to find a highly significant correlation between EGFR FISH and IHC in NSCLC. This suggest that clinical use of these tests may be highly reproducible and can be safely performed before treating patient with EGFR tyrosine kinase inhibitors. Other markers such as E-cadherin and desmoglein 3 are tested presently.

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Effect of gefitinib on survival of patients with pulmonary adenocarcinoma who had recurred after surgery in case controlled study.

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Background: Large international randomized trial (ISEL) failed to show survival advantage of gefitinib over placebo in patients with non-small lung cancer (NSCLC) who failed standard chemotherapy. However, a subset of patients with NSCLC, especially those of East Asian origin, female gender, never-smokers and adenocarcinoma respond dramatically well to gefitinb. The purpose of this study was to evaluate whether gefitinib could improve the prognosis of the lung adenocarcinoma patients with post-operative recurrence compared with other chemotherapeutic agents using a case control study.