TTP and OS were female gender, the absence of smoking history, and adenocarcinoma histology. As expected, those treated with Erlotinib in the first line setting had significantly longer TTP than further lines (7.4 vs. 4.4; p<0.001). In the multivariate analysis only non smoking history remained as predictive factor for longer TTP and survival (p<0.0001). Most frequent reported adverse events were rash (62.9%; 12.9% grade 3/4), asthenia (37.1%; 9.2% grade 3/4) and diarrhea (33.3%; 6.1% grade 3/4).

Conclusions: This interim analysis of a subset of elderly patients with advanced or metastatic NSCLC treated with Erlotinib in a real-life clinical setting confirms the good tolerability and promising activity. It is worthwhile mentioning the benefit in survival obtained by chemonaive elderly patients. Therefore Erlotinib is an effective treatment for elderly patients with advanced NSCLC, even as a first-line treatment. A randomized phase III study intended for elderly patients with Erlotinib is warranted.

P3-062 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Wood-smoke exposure as a survival predictor in non-small cell lung cancer with response to erlotinib: an open label phase II study

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Background: Erlotinib, a tyrosine kinase inhibitor, has been shown to improve the survival and quality of life in patients with non-small cell lung cancer (NSCLC) after first or second-line chemotherapy. Asian origin, adenocarcinoma histologic type, female gender, lack of tobacco use, and expression of EGFR have been described as significant independent predictors of response to erlotinib. Although tobacco use is considered a major cause of NSCLC, other factors are involved in its pathogenesis. In underdeveloped countries such as Mexico, wood and other solid fuels are still used for cooking and heating. The pathophysiological mechanisms of wood smoke exposure (WSE) as a potential risk factor for the development of NSCLC are still unknown.

Methods: In this study, 135 patients with histologically proven NSCLC with poor performance status were treated with erlotinib after first or second-line chemotherapy. Clinical and pathological characteristics were associated with response to treatment.

Results: We found a global response to erlotinib in 45 patients (31.3%, CI 95% 23.5-39.1), stable disease in 31.9% and progression in 30.6%. Clinical improvement was observed in 56.5%. The clinical features associated with response to erlotinib in the univariate analysis were female gender (44.4 vs. 20.6%, p=0.003), no tobacco use (48.4 vs. 19.7%, p<0.001). Borderline statistical significance was observed with adenocarcinoma histological type (34.3 vs. 16%, p=0.086). However, in the logistic regression analysis only the histological type (p=0.049) and WSE (p=0.001) showed statistical significance. The factors associated to an improved progression-free survival (PFS) in the Cox multivariate analysis were adenocarcinoma histologic type (7.9±0.7 vs 2.2±0.4 months, p= 0.02), female gender (8.4±0.7 vs 4.4±1.6 months, p= 0.02) and WSE (17.56±4.17 vs 4.8±0.7 months, p< 0.001).

Conclusion: WSE is associated with response to erlotinib in patients with NSCLC and may indicate an improvement in PFS. The EGFR mutation is probably involved in the development of NSCLC in non-smokers with WSE.

P3-063 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

The role of IL-20 in lung cancer: A new epigenetic target?

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Background: IL-20 is a pleiotrophic member of the IL-10 family and plays a role in skin inflammation and the development of haematopoietic cells. It has potent angiogenic, inflammatory and chemo-attractive characteristics with an involvement in rheumatoid arthritis and atherosclerosis. It activates STAT3, which in turn promotes proliferation, apoptosis resistance and immune tolerance. STAT3 activation is recognised as an important link between inflammation and cancer. It can function through IL-20Rα, IL-20Rβ and IL-22R1. Decreased expression of IL-20Rα in lung tissues of non-small lung cancer patients correlated with an increase in disease free survival.

Methods: A panel of cell lines were examined for the expression of IL-20, IL-20Rα and IL-20Rβ at the mRNA and protein level. This included three normal (HBEC 3, 4 & 5) and two lung cancer (A549- adenocarcinoma & SK-MES-1- squamous cell carcinoma) cell lines. The effects of a histone deacetylase inhibitor, Trichostatin A, (TSA-250ng/ml) and cycloheximide (10μg/ml) on the expression of IL-20Rα among a number of normal and lung cancer cell lines were examined. A CHIP assay was carried out to investigate the effect of TSA on the IL-20 promoter. Tumour and normal matched tissue from patients were examined at the mRNA and protein level for the IL-20 receptors.

Results: The mRNA expression pattern of IL-20 was different in the normal and lung cancer cell lines. There was moderate to high expression in the three normal cell lines compared with low to moderate levels in the cancer cell lines. A similar trend was observed with IL-20Rα and IL-20Rβ. The anti-angiogenic properties of IL-20 have previously been demonstrated in the lung. We investigated the effect of TSA on IL-20 expression. IL-20 was induced by TSA treatment in all cell lines and super-induced by cycloheximide in A549 and HBEC 4. Results from a CHIP assay performed on A549 cells demonstrates that the effect of TSA is and early and immediate response. The effect of TSA on the two receptors at mRNA level was much less pronounced on the cell lines with the exception of HBEC 4, which showed a minor increase of both with treatment. Further analysis of IL-20 and the receptors in clinical (adenocarcinoma and squamous cell carcinoma) samples revealed a somewhat different pattern between the two lung cancer types. At the mRNA level, IL-20 was downregulated in adenocarcinoma and upregulated in squamous samples. There was an increase in IL-20Rβ mRNA and protein in both tumour types. A significant difference was observed in IL-20Rα expression between the tumour types. In adenocarcinomas, IL-20Rα was predominantly downregulated at the mRNA level, with minimum detection at the protein level. However, in squamous samples the receptor was upregulated in tumours at both the mRNA and protein level.
Conclusions: An IL-20 ELISA has been developed and further samples are being collected for analysis. Based on these findings that IL-20 is up-regulated by TSA and under epigenetic control, targeting this cytokine may be used as a potential anti-angiogenic approach in making lung cancer history.

P3-064  NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Gefitinib (Gefitinat) in advanced non small cell lung cancer: a follow up observation in Indian patients

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A number of growth-factor-receptor-targeted agents have been tried with encouraging results in patients with advanced NSCLC (Noble et al 2006). Women, non-smokers, adenocarcinoma and Asians respond better. This communication is our further experience of our earlier presentation.

Histologically proven advanced (stage IIIIB or IV) non-small cell lung cancer patients earlier treated with chemotherapy received gefitinib (Gefitinat) 250mg daily orally. There were 28 females (38-57 yrs) and 67 males (44-67 yrs). Fifty four were non-smokers and the remaining were smokers. Sixty two had adenocarcinoma and 33 had squamous cell carcinoma. The disease was of stage IIIIB (n=58) and stage IV (n=37). The duration of gefitinib therapy varied from 20 weeks to 58 weeks with median of 29.5 weeks. The disease remained static in 66% (69%) with stabilization or improvement in the Kornofsky performance scales in 73%. The mean performance status improved from 70 to 90 in 34 cases, deteriorated in 13 and in the remaining remained static at 90. There was no radiological progression in 43 cases, while 28 cases showed radiological progression. The median survival (calculated after completion of chemotherapy and start of gefitinib) was 33 weeks with 22 patients surviving beyond 1 year. The drug was well tolerated by all. Thirty three patients complained of mild skin rash (three fixed drug eruption). 29 patients had grade 1-2 diarrhoea.

We found gefitinib as beneficial. The drug is well tolerated by Indian patients. This may be due to a different pharmacogenomic property of gefitinib in this population.

P3-065  NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

A lead-in safety study of erlotinib combined with sunitinib for the treatment of metastatic non-small cell lung cancer (NSCLC)

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Background: VEGF expression has been correlated with increased tumor angiogenesis and shortened survival in NSCLC, and inhibition of the VEGF and also the EGFR signaling pathways has a demonstrated treatment benefit in this malignancy. Therefore, a treatment strategy combining agents that specifically inhibit both signaling pathways may further improve patient outcome. Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3, approved multinationaly for the treatment of advanced renal cell carcinoma and imatinib-resistant or -intolerant gastrointestinal stromal tumor. A multicenter phase II trial of sunitinib administered on a 4/2 schedule (4 weeks on treatment followed by 2 weeks off) in recurrent advanced NSCLC demonstrated an 11% objective response rate among patients treated second- or third-line (Socinski, ESMO 2006). Here we report the results of a lead-in safety study assessing the safety and tolerability of sunitinib combined with erlotinib in locally advanced or metastatic NSCLC after failure of chemotherapy. If the safety profile of the combination is favorable, 126 patients will be randomized to sunitinib plus erlotinib or to placebo plus erlotinib in a phase II portion of the study.

Methods: The lead-in safety cohort was planned to include 10 patients evaluable for the safety and tolerability of sunitinib combined with erlotinib, with additional patients enrolled if needed to obtain adequate pharmacokinetic data. Patients were eligible if they had histologically proven, stage IIIIB or IV NSCLC; had received 1 or 2 prior chemotherapy regimens, including a platinum-based regimen; measurable disease; ECOG PS 0 or 1, and adequate organ function. Treatment comprised sunitinib 37.5 mg/day continuously plus erlotinib 150 mg/day, given orally, in repeated 4-week cycles. Patients were observed for dose-limiting toxicities (DLTs) during the first 28 days of treatment.

Results: Twelve patients were treated in the lead-in cohort, with the following baseline characteristics: median age 62 years (range 47-75); 6 male; histology 9 adenocarcinoma, 1 squamous cell carcinoma, 2 other; history of smoking in 8 patients. The patients started a median of 2 cycles (range 1-5), with dose reductions in 5 patients (erlotinib, n=2; sunitinib, n=1; both, n=2). Two patients developed a DLT (both grade 3 fatigue lasting at least 7 days). Adverse events were generally mild-to-moderate in severity (grade 1/2). Seven patients experienced grade 3 adverse events that included diarrhea (n=3), fatigue (n=2), acne (n=1), anemia (n=1), dehydration (n=1), diffuse skin rash (n=1), pruritus (n=1) and paronychial inflammation (n=1); no grade 4/5 events were reported. Pharmacokinetic analyses are ongoing.

Conclusions: Sunitinib 37.5 mg/day given continuously with erlotinib 150 mg/day was safe and tolerable in this cohort of patients with advanced NSCLC. The efficacy and safety of sunitinib combined with erlotinib will be investigated further in the randomized phase II portion of this study.

P3-066  NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

The potential predictive value of cyclooxygenase-2 expression and increased risk of gastrointestinal hemorrhage in advanced non-small cell lung cancer patients treated with erlotinib and celecoxib

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Background: In non-small cell lung cancer (NSCLC) preclinical models, celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, potentiates the apoptotic and growth inhibitory effects of erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). We designed a phase II trial to evaluate the clinical efficacy and safety of erlotinib plus celecoxib in advanced NSCLC.