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Erlotinib as a second-line therapy in advanced non small cell lung cancer: correlation between clinical characteristics and biomarkers

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Background: Inhibition of the epidermal growth factor receptor (EGFR) pathway with small molecule tyrosine kinase inhibitors (TKI), as erlotinib, can improve outcome of patients (pts) with non small cell lung cancer (NSCLC) who have progressive disease after treatment with cytotoxic chemotherapy. The use of clinical and molecular factors may permit the identification of patients who are most likely to benefit from erlotinib.
Material and Methods: Pts with stage IV NSCLC who had previously failed on first or second line chemotherapy received erlotinib 150 mg/die p.o. until disease progression or unacceptable toxicities. DNA was extracted from formalin-fixed paraffin-embedded tissues or from cytologic samples and was screened for EGFR (exon 19 and 21) and K-ras mutations (codon 12 and 13) with high resolution melting analysis (HRMA); mutations were identify through sequencing. Clinical outcomes were assessed in relation to clinical characteristics (sex, smoke, histology) and biomarker status (K-ras and EGFR mutations).
Results: 53 pts were recruited from May 2006 to February 2009: median age 65 yrs (range:37−81); female 19(36%); never-smokers 7(13%); adenocarcinoma/squamous cell/other 29(55%)/13(25%)/11(20%); K-ras mutated(mt)/K-ras wild-type(wt) 13 (25%)/35(66%); EGFR mt exon 19/exon 21 6(11%)/2(4%); 2nd-line/3rd-line/other 28(53%)/19(36%)/6(11%). Pts with best response were 6 (11%); 14 (26%) pts had stable disease and 29 (55%) pts had progressive disease. The overall disease control rate (ODCR = CR+PR+SD) was 37%. Progression free survival (PFS) was 3 months and median survival (OS) was 7 months. In 17 (32%) pts erlotinib was reduced for toxicity.
The ODCR was significantly increased in pts never-smokers (100% vs 33% in smokers, $p = 0.0016$) and in pts with EGFR mutations (100% vs 31% in EGFR wt, $p = 0.004$). Pts never-smokers or with EGFR mutations had significantly longer PFS (never-smokers vs smokers: 20 vs 3 months, $p = 0.006$; EGFR mt vs EGFR wt: 18 vs 3 months, $p = 0.004$). OS analysis was in progress. Outcome was not significantly influenced by sex, histology and K-ras mutations.
Conclusions: In our experience only EGFR mutations and never-smoker status were prognostic factors for disease control and PFS These data do not support selection of patients for treatment with erlotinib on the basis of other clinical or molecular characteristics.

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Phase Ib trial (NCT00619424, VEG109607) of pazopanib (GW786034) and erlotinib administered concurrently

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Background: Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit with demonstrated activity in early-stage non-small cell lung (NSCLC) cancer, renal cell carcinoma, sarcoma, and ovarian cancer. Erlotinib is an oral inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. The capacity to inhibit both the VEGF and the EGF pathways, coupled with encouraging clinical results in advanced NSCLC with a regimen of bevacizumab and erlotinib, supports combining pazopanib and erlotinib.
Methods: Patients (ECOG PS 0−1) with advanced cancer where erlotinib is standard therapy or where no additional standard therapy options exist were eligible. Escalating doses of pazopanib (400−800 mg once daily) plus erlotinib (100−150 mg once daily) were evaluated in cohorts of 3−6 patients for safety to identify a maximum tolerated dose (MTD) and for preliminary evidence of clinical activity. Twelve additional patients were to be enrolled in an expansion cohort to confirm the MTD. Adverse events (AEs) were evaluated according to NCI CTCAE v3.0.
Results: A total of 20 patients (median age 64 yrs) received continuous daily dosing of pazopanib/erlotinib at doses of 400 mg/100 mg (n = 7), 400 mg/150 mg (n = 3), 600 mg/150 mg (n = 6), and 800 mg/150 mg (n = 4). Most common tumor types were NSCLC (n = 10), thyroid (n = 2), and colorectal cancer (n = 2). Most frequent AEs were rash (n = 13), diarrhea (n = 10), decreased appetite (n = 10), nausea (n = 8), fatigue (n = 7), AST elevation (n = 8), and hypertension (n = 6). All were Gr 1/2, except Gr 3 rash (n = 1) and nausea (n = 1)and AST elevation (n = 1); The MTD was defined as 600 mg pazopanib and 150 mg erlotinib. No DLTs were observed at this dose. Two DLTs (severe rash and elevated liver function tests) were observed at 800 mg pazopanib and 150 mg erlotinib. A Gr 5 SAE of subacute encephalopathy was reported in the 400 mg pazopanib and 150 mg erlotinib cohort 3 days after drug interruption at patient request. This event was considered unrelated to study treatment. Best response of partial response was reported in 3 patients (all NSCLC; i.e., 3/10 NSCLC patients), while stable disease of $\geqslant$12 weeks was reported in 4 patients (n = 1 for each: gastroesophageal junction, liver, NSCLC, ovarian). Data from the expansion cohort will also be presented.
Conclusion: Concomitant administration of pazopanib 600 mg and erlotinib 150 mg is feasible with a manageable toxicity profile and preliminary evidence of clinical activity.

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Prognostic model to predict outcomes in non-small cell lung cancer patients treated with erlotinib as a salvage treatment

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Purpose: To devise a prognostic model based on clinical parameters for non-small cell lung cancer (NSCLC) patients treated with erlotinib as a salvage therapy.
Patients and Methods: Between July, 2006 and September, 2008, 257 metastatic or relapsed NSCLC patients who had been treated with erlotinib as a salvage therapy were analyzed retrospectively.
Results: For the 257 patients, the median overall survival (OS) and the progression free survival (PFS) since the start of the salvage erlotinib were 12.4 months and 2.8 months. Multivariate analysis showed that ECOG performance 2−3, elevated serum LDH level, and no skin rash were independent adverse prognostic factor for OS and presence of intra-abdominal metastasis, prior chemotherapy $\geqslant$ 2, and no skin rash for PFS. OS and PFS were estimated on the basis of each adverse prognostic factors: zero (good prognostic group), one (intermediate group), two (poor prognostic group), and three (very poor prognostic group). OS and PFS were significantly reduced with a greater number of adverse predictive factors. The median OS since the start of the salvage erlotinib for good, intermediate, poor, and very poor prognostic group were 22.0, 9.3, 5.4, and 2.7 months, respectively ($p < 0.001$) and the median PFS were 6.5, 3.0, 1.2, and 0.9 months, respectively ($p < 0.001$).
Conclusion: This prognostic model based on easily available variables would be useful to identify patients who might derive more benefit from erlotinib therapy and to make decision in clinical practice.

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Lapatinib as maintainence treatment after first line treatment of metastatic adenocarcinomas of lung in never smokers or seldom smokers

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Background: Her 2 overexpression is known to be a poor prognostic marker in lung cancer. It is seen in 11−33% of NSCLC (Non Small Cell Lung Cancer). There are reports of responses to Trastuzumab treatment in NSCLC. Her 2 Pathway is also implicated in a cross talk causing resistance to EGFR inhibitors. There is good rationale to consider dual blockade of Her 2 and EGFR in NSCLC in seldom or never smokers as we have learnt from our experience with Erlotinib. This study was designed to assess the efficacy of Lapatinib as maintainence treatment in advanced NSCLC.
Materials and Methods: From September 2007 to November 2008, 40 patients of metastatic adenocarcinomas of lung who were never or seldom smokers and who had at least a partial response with 4 cycles of Paclitaxel and Carboplatin were randomized to maintainence with either Lapatinib 1000 mg/d for 6 months or observation alone. Patients were assessed for further tumor responses, progression free survival, adverse events and quality of life functions.
Results: Out of 40 patients 19 were males and 21 females. Both arms were well matched for disease stage, performance status, age and also the degree of response to chemotherapy. In the Lapatinib maintainence arm, 12/20 patients (60%) had further partial responses and 4/20 patients (20%) had stable disease. 4/20 patients (20%) had progressive disease. In chemotherapy followed by observation only arm 0/20 patients had