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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

further responses while 9/20 patients (45%) had stable disease. 11/20 patients (55%) had progressive disease. The partial response plus stable disease rates were significantly more in Lapatinib arm (p = 0.001). Median progression free survival for observation alone arm was 4.8 months while that for lapatinib arm has not yet been reached. Another interesting finding was incidence of brain metastasis which was 0/20 in lapatinib maintainence arm while it was 4/20 in observation alone arm. The treatment was well tolerated in both arms with no major skin rash and cardiotoxicity seen with Lapatinib. Encouraged by these responses we are in a process of analyzing the EGFR mutation status and Her 2 overexpression in available tissue specimens.
Conclusion: There is good rationale to use dual blockade of Her2 and EGFR after chemotherapy in Adenocarinomas of lung in seldom or never smokers. As found in this study, it may translate into better tumor responses, reduction in brain metastasis and better survival. This hypothesis needs testing in large multicenter trials.

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Evaluation of treatment adherence, persistance, and quality of life in patients with advanced non-small cell lung cancer (ANSCLC) treated with erlotinib (e) as second-line therapy

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Background: Patients (pts) adherence and persistence to oral antitumoral treatments may vary considerably and is an issue generally difficult to monitor. Compliance to oral therapies may therefore be quite low hampering potentially successful treatments and rising safety issues. Compliance has been defined as "the degree or extent of conformity to the reccomendations about day-to-day treatment by the provider with respect to timing, dosage and frequency" and its also called adherence which should be distinguished form persistence which is the duration of time from the initiation to the discontinuation of treatment. In this paper we report our experience on treatment adherence, persistence and QOL of pts with ANSCLC treated with second-line E before and after an institutional proactive management.
Materials and Methods: Our program of evaluation of quality of cancer care included a specific chapter on the management of oral antitumoral agents. Attending oncologists were required to assess the critical problems of pts treated with seond-line E before the development of a specifically dedicated oral therapy unit (cohort 1), and to monitor pts adherence and persistence to E in a second group of pts (cohort 2) managed throught specific counseling with pts and main caregivers, written detailed prescription and the use of a dedicated fax-line. All pts were previously treated with cisplatin-based chemotherapy and had progressive cancer at the beginning of E 150 mg/day. Pts were restaged after 2 months and closely monitored for side-effects.
Results: In the first cohort of 28/50 pts reported low adherence and persistence to E not correlated to medical reasons (i.e. side-effects or other conditions requiring dose reduction). Perceived assistance by pts and families was unsatisfactory in 58% of cases. In the second cohort of 50 pts the level of treatment adherence, persistence of therapy and perceived assistance were significantly improved as compared to cohort 1. Also the management of side-effects was easier in the cohort 2. QOL data are still in progress.
Conclusions: The institution of an oral unit with specific counseling with both pts and their family caregivers as well as the creation of a a dedicated fax line is play a pivotal role in the management of pts with ANSCLC treated with E as second-line therapy. In this setting of patients with relatively short median survival the manteinance of adherence to treatment throught the optimization of pts management is of paramount importance.

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Volociximab (V) in combination with carboplatin (C) and paclitaxel (P) in patients (pts) with advanced non small cell lung cancer (NSCLC)

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Background: Volociximab is a chimeric monoclonal antibody that blocks the binding of a5b1 to fibronectin and induces apoptosis in proliferating endothelial cells. Its anti-angiogenic actions are independent of the VEGF pathway.
Methods: This phase 1b multi-center open-label, dose-escalation study was designed to determine the maximum tolerated dose of V in combination with full doses of C (AUC = 6 mg/ml·min) P (200 mg/m^2) with cycles repeated every 3 wks for a maximum of 6 cycles followed by a maintenance treatment with V alone. Eligible pts had histologically confirmed untreated stage IIIb or IV NSCLC. In cohorts 1 and 2, pts received V at 10 mg/kg and 20 mg/kg IV, respectively, on days 1 and 8, of the first 21 day cycle then every 21 days. In cohort 3, pts received V 30 mg/kg every 21 days from day 1.
Results: A total of 33 pts were enrolled, screening ECOG PS_0 = 19(58%), PS_1 = 13(39%), missing = 1(3%), predominant histology: adenocarcinoma 23 (70%), large cell 4 (12%), squamous cell 5 (15%), and missing 1 (3%). 29 pts (9, 6 and 14 in cohorts 1, 2 and 3 respectively) who received at least one dose of treatment were included in the safety evaluable population. No pts experienced hemoptysis including 5 (15%) pts with squamous cell carcinoma. The majority of adverse events were mild to moderate and the most common AEs of any grade were constipation (62%), asthenia (59%), nausea (59%), arthralgia (52%), diarrhea (48%), paresthesia (48%), vomiting (41%), myalgia (41%), abdominal pain (38%), peripheral neuropathy (38%), anorexia (38%) and cough (38%). Serious AEs in 8 (28%) pts include back pain (1), bronchitis (1), deep vein thrombosis (1), dehydration (1), peripheral arterial occlusion (1), pleural effusion (1), pneumonitis (1), proteinuria grade 3 (1), orthostatic hypotension (1), and small intestinal obstruction (1) which was a DLT in the 20 mg/kg dose cohort. No DLT was observed at the highest dose of 30 mg/kg. Preliminary PK analysis demonstrated that the average steady state trough levels of V across all dose groups were above 150 mcg/mL, the efficacious serum concentration based on preclinical xenograft model, and are proportional to doses. Preliminary efficacy assessment in evaluable pts who had at least one post-baseline RECIST assessment showed 8/21 (38%) with a partial response and 13/21 (62%) had stable disease. 14/21 (67%) with SD or PR continued on maintenance V beyond 6 cycles of chemotherapy with CP.
Conclusions: V up to 30 mg/kg q3w in combination with CP and as maintenance after six cycles appears to be well tolerated and has promising clinical activity in pts with both squamous and non-squamous histologies of NSCLC.

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A phase II study of gefitinib monotherapy as first-line treatment for elderly patients with stage IIIB /IV adenocarcinoma of the lung

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Background: Gefitinib is active in previously treated patients with advanced non-small cell lung cancer. We assessed the efficacy and safety of gefitinib as first-line therapy in elderly patients with advanced adenocarcinoma of the lung in a phase II study.
Patients and Methods: Chemotherapy-naive patients who were 70 years old or older with stage IIIB or IV adenocarcinoma of the lung were treated with oral gefitinib 250 mg daily until disease progression or unacceptable toxicity occurred. The primary endpoint was response rate. Testing for epidermal growth factor receptor (EGFR) and KRAS mutations was performed when tumor specimens were available.
Results: Of 32 patients enrolled, 30 were assessable for response and survival. Eight patients achieved partial response (PR) and seven had stable disease (SD) with an objective response rate of 27% (95% CI, 12−46%) and disease control rate (PR + SD) of 50% (95% CI, 31−69%). Never-smoker patients and female patients had higher response rates (33 vs 17%, 35 vs 10%, respectively). The results of EGFR and KRAS mutation testing were available in 10 patients. Of 10 patients, four harbored EGFR mutations and all of them achieved PR. KRAS mutation was detected in none of these 10 patients. The median survival time for all patients was 12.4 months. The median progression-free survival was 2.5 months. Grade $\geqslant$ 3 pneumonitis was observed in two patients. Other toxicities were generally mild.
Conclusions: Gefitinib monotherapy is active and well-tolerated as first line treatment in elderly patients with advanced adenocarcinoma of the lung.