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A multi-centre randomized, open-label phase II trial of erlotinib plus gemcitabine or gemcitabine monotherapy as first-line therapy in ECOG PS2 patients with chemo-naive advanced NSCLC

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which is the main organ of erlotinib metabolism (Cancer Research, 2009 69: 873-878).

We have now extended this study to patients with the aim to identify the subset of patients that will respond to Erlotinib treatment (10-15 %). Tumors were identified by routine CT scan and [18F]-2-fluoro-2-deoxyglucose (FDG) PET/CT and compared with [11C] erlotinib PET/CT. As expected, all patients examined so far (n=4) showed [18F] FDG uptake. Our results with [11C] erlotinib show that tumors can be identified by [11C] erlotinib. However we do not know yet if this accumulation can be used to identify the subgroup of patients responding to erlotinib.

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Background: The majority of research effort in advanced NSCLC has focused on patients with good performance status (ECOG PS 0-1). Treatment of patients with ECOG PS 2 is poorly defined. Erlotinib, a selective inhibitor of EGFR tyrosine kinase, is currently approved for the use in the treatment of NSCLC after failure of platinum containing therapy. Gemcitabine has been successfully combined with erlotinib in patients with advanced pancreatic cancer with improved efficacy. The aim of this study was to assess the activity and tolerance of the combination of gemcitabine + erlotinib in patients with chemonaive NSCLC who are ECOG PS2.

Methods: Eligible patients had chemotherapy-naive NSCLC either stage IIIB (with plural effusion) or stage IV with measurable disease and ECOG PS 2, and adequate organ function. Patients were randomized to receive either erlotinib (150 mg/day p.o.) plus gemcitabine (1000 mg/m^2 Day 1,8 +15 q28 days), (EG), or gemcitabine monotherapy (1000 mg/m^2 Day 1,8 +15 q28 days), (G). Recruitment over a 12 month period was slow due to a lower than expected number of suitable ECOG PS 2 patients. Consequently the study was closed early.

Results: A total of 17 patients (pts) were randomized (12 male, 16 current or former smokers, 4 squamous cell, 4 large cell and 9 adenocarcinoma). Sixteen pts received treatment (each arm n = 8). Incidence of treatment-related adverse events (AEs) was n = 8/8 in the EG arm and 6/8 in the G arm (n=number of pts). Most AEs were grade 1-2. No difference in the number of treatment-related hematological toxicities was seen (each arm, n = 3/8). The most common treatment-related non-hematological AEs in the EG arm were rash (n = 7/8) and diarrhea (n = 7/8), most of which were grade 1-2. No treatment-related rash or diarrhea was reported in the G arm. No pts withdrew due to treatment-related AEs. Efficacy was evaluable in 15 pts (1 patient received no treatment in G arm, 1 patient in EG arm had no follow-up tumor assessment). The best overall response was partial response (PR) in 2 pts in the EG arm (duration of response was 16 and 47+ weeks, respectively), with no responses seen in the G arm. Both responders were former smokers, one male and one female, with squamous cell and large cell carcinoma respectively. At 8 and 16 weeks, 6/7 and 3/7 pts in the EG arm and 6/8 and 2/8 pts in the G arm, respectively, had not progressed.

Conclusion: The investigated regimen of erlotinib in combination with gemcitabine for the treatment of advanced stage, chemotherapy-naive NSCLC ECOG PS 2 patients seems to be feasible with acceptable toxicity. No new safety signals were identified for erlotinib. Although the observed PR in the combination arm of this difficult to treat patient population is encouraging, the efficacy of adding erlotinib to gemcitabine therapy needs to be further evaluated. Further investigations which allow for the inclusion of a wider patient-population (ECOG PS 2 and elderly) and which combines intercalated administration of erlotinib and gemcitabine are ongoing.

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A randomized phase II study comparing a 21-day schedule of Pemetrexed (P) and Gemcitabine (G) versus biweekly P and G in patients with advanced Non-Small Cell Lung Cancer (NSCLC)

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Background: Pemetrexed (P), a multi-targeted antifolate, is synergisitic with gemcitabine (G) in preclinical models. Among patients with advanced NSCLC, the combination has been shown to have activity in several Phase II trials employing 21-day treatment cycles (West et al. Ann Oncol 2009, Treat et al. Lung Cancer 2006, Ma et al. JCO 2005, Monnerat et al. CCR 2004) and in one trial employing a 14-day treatment cycle (Dudek et al. JTO 2008). The current randomized trial was initiated to investigate the optimal scheduling of P plus G in advanced NSCLC.

Methods: Patients with Stage IIIB (with pleural effusion) or IV NSCLC, ECOG performance status (PS) of 0 or 1, no prior systemic chemotherapy, immunotherapy, or biological therapy were enrolled. Treatment consisted of P 500 mg/m^2 followed by G 1250 mg/m^2 on Days 1 and 8 repeated every 21 days, up to 6 cycles (Arm A) or P 500 mg/m^2 followed by G 1500 mg/m^2 on Day 1 every 14 days, up to 9 cycles (Arm B). All patients received folic acid, vitamin B12, and steroid prophylaxis. The primary endpoint was response rate. Planned sample size was 80 patients.

Results: Between 2/07 and 1/08, 19 patients were enrolled (10 in Arm A and 9 in Arm B). This trial was subsequently discontinued prior to achieving the full planned sample size. One patient (Arm B) was not included in efficacy analysis due to a protocol violation.

Conclusion: Every 21-day or biweekly schedules of G and P appear to be well tolerated in advanced NSCLC. Early termination of this trial precludes definitive conclusions.