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Phase II study of erlotinib (E) with or without sunitinib (SU) in the treatment of metastatic non-small cell lung cancer (NSCLC)

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Background: Inhibitors of EGFR or VEGF signaling have demonstrated benefit in the treatment of patients (pts) with NSCLC. Thus, a novel treatment strategy of co-inhibition of EGFR and VEGF may provide significant benefit over inhibition of either signaling pathway alone. SU is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, and FLT3, approved internationally for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST. In a phase II study of pts with treatment-refractory NSCLC, sunitinib monotherapy demonstrated an 11.1% confirmed objective response rate. The present study was designed to examine the efficacy and safety/tolerability of E $\pm$ SU in pts with platinum-refractory NSCLC.
Materials and Methods: In this double-blind, multicenter, phase II trial, pts with stage IIIB/IV NSCLC, ECOG PS 0–1, adequate organ function, and who had received prior treatment with a platinum-based regimen are randomized to receive treatment with either SU + E or placebo + E. Prior to initiating the phase II portion, a lead-in safety study was conducted in which pts were assessed for safety following treatment with SU at 37.5 mg/d (dosed continuously) and E 150 mg/d; in addition, full pharmacokinetic (PK) profiles were performed. If there were $\leqslant$3 dose-limiting toxicities (DLTs) excluding dyspnea and $\leqslant$4 DLTs including dyspnea during a 28-day treatment period with E + SU, then the randomized study could proceed. Additional pts could be added to the lead-in study if <6 pts completed full PK sampling.
Results: In the lead-in cohort, 12 pts were treated with SU 37.5 mg/d continuously + E 150 mg/d po in 4-wk treatment cycles and were observed for DLTs during the first 28 d of treatment. Baseline characteristics: mean age 63 yrs (range 47−75); 6M/6F; histology 11 adeno/1 squamous; smoking history 8 yes/4 no. Median cycles started were 2 (range 1–5) with dose reductions in 6 pts (E, n = 3; SU, n = 2; both, n = 1). Two pts developed a DLT (Grade [G] 3 fatigue $\geqslant$7 d). Most AEs were mild-to-moderate in severity (G 1–2). The most common grade 3 AEs included diarrhea (n = 4) and fatigue (n = 2). One pt experienced G4 fungal pneumonia and sepsis. To date 1 pt has a durable confirmed PR. PK study for both drugs is ongoing.
Conclusions: SU 37.5 mg/d given continuously with 150 mg/d E is safe and tolerable in this pt population and will be further investigated in the randomized phase II portion of this study, which is enrolling.

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Analysis of possible relationships between tumour biomarkers and clinical benefit from erlotinib in advanced non-small cell lung cancer (NSCLC): data from the prospective MERIT study

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Background: The oral EGFR tyrosine-kinase inhibitor erlotinib (Tarceva®) significantly prolongs survival, delays symptom progression and improves quality of life, as demonstrated in the placebo-controlled BR.21 trial. Neither EGFR expression status, gene copy number nor mutation status predicted survival in post-hoc multivariate analyses. The multi-centre, open-label phase II MERIT study prospectively investigated potential molecular markers to predict clinical benefit with erlotinib and is the largest biomarker study ever performed in NSCLC.
Methods: Patients (pts) with advanced (stage IIIb/IV) NSCLC, ECOG PS 0–2, $\geqslant$18 yrs old, with $\geqslant$1 failed chemotherapy (CT) regimen (or unsuitable for/refused CT) were eligible for MERIT. Tumour biopsies had to be performed by bronchoscopy before starting treatment. Erlotinib (150 mg/day p.o.) was given until progression, death or unacceptable toxicity, with dose reductions allowed for adverse events (AEs). Tumour response and tolerability were regularly assessed. Laser capture microdissection was used to isolate tumour cells from the fresh-frozen biopsies, from which RNA was then purified. Affymetrix Human U133A microarrays were used to analyse gene expression profiles in these RNA samples. Other biopsy samples were analysed using IHC for EGFR and downstream signalling molecules. EGFR mutations were identified by DNA sequencing and gene copy number was determined using FISH.
Results: A total of 264 pts in 12 countries (median age 61 yrs) had available efficacy data: 70% were male; 74% had stage IV disease; 38% were Asian; 73% were ever-smokers; ECOG PS was 0 in 13%, 1 in 64% and 2 in 23%; 49% were 2nd line, 27% 3rd line and 24% 1st line. 36 pts (14%) had an objective response (RECIST); clinical benefit (response or SD > 12 weeks) was seen in 83 pts (31%). Median overall survival was 7.6 mths while progression-free survival was 11.3 wks. 88% of 257 pts with safety data had at least one AE, and 24% had a serious AE. The most common AEs were rash, diarrhoea, dyspnoea and anorexia. Treatment was discontinued due to AEs in 6% of patients, and 12% had dose reductions. Material for gene expression profiling was available for 122 pts.
Conclusions: Early data from the MERIT study support the use of erlotinib as an effective, well-tolerated alternative to chemotherapy for patients with advanced NSCLC who have failed $\geqslant$1 previous chemotherapy regimen. Analyses regarding biomarkers and clinical benefit with erlotinib will be presented.

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A phase II study of erlotinib (E) and bevacizumab (B) in patients (pts) with previously untreated stage IIIB/IV non-small-cell lung cancer (NSCLC)

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Background: In advanced NSCLC, E and B either as a single agent (E) or in combination with chemotherapy (B) have shown to improve survival. Combinations of targeted agents may prove to be effective and better tolerated than chemotherapy.
Methods: This is a multicenter 2-stage phase II study (Simon's optimal design; p0 = 40%, p1 = 60%, a = 0.05, b = 0.20) with early stopping rule. The primary endpoint is non-progression (NPR) at 6 weeks. When 24/46 pts have NPR at 6 wks the treatment will be declared to have sufficient activity for further testing.
Pts (PS 0–2) with advanced non-squamous NSCLC who had received no prior systemic anti-tumour therapy were treated with E (150 mg/day) plus B (15 mg/kg every 21 days) until disease progression or unacceptable toxicity, An imaging protocol including CT, DCE-MRI and FDG/H20 PET was performed at weeks −1, 3 and 6.
Results: Between 02/06 and 04/07 50 pts were included (3 screen failures, one early death); 33 pts already evaluable for efficacy and safety. Demographics: M/F: 17/16; median age 60 (range 34−80); PS 0/1/2: 16/13/4; smoking status: current/former/never 13/16/4. Twenty-five pts had stage IV disease. The most common treatment-related adverse events (all grades) were: rash (47%) and diarrhea (47%). Hypertension was observed in 9.4% of patients. Grade 3/4 adverse events ($\geqslant$5%) consisted of rash (31% of pts). There was 1 probable treatment-related death. (pt died 15 days after start treatment for unknown reason). Six pts withdrew early from the study, 2 due to toxicity (trombosis and mucositis), 2 due to death (1 death for unknown reason, 1 due to pneumonia), 2 for treatment unrelated reasons. 5 pts had E dose modifications for toxicity and 5 delay of B mainly for logistic reasons.
Rate of NPR at 6 weeks 76% (25/33) with 10 (30%) PR. The median follow-up is 7.2 months (95% CI 4.3−8.6 months). Median TTP: 5.5 months (95% CI 1.3−6.2), At this interim analysis 22/33 patients are alive, 16/31 patients are without disease progression and 13/32 patients are on protocol treatment.
Conclusions: E + B was well tolerated, with a low rate of grade 3/4 adverse events and no unexpected toxicities. The 75% no progression rate justifies phase III testing in untreated advanced non-squamous NSCLC against platinum based chemotherapy. Final results including correlative imaging studies will be presented.