6606 POSTER

Three drug regimen in SCLC-ED patients: a phase II study

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Background: Small cell lung cancer (SCLC) is an aggressive malignancy. The prognosis for the patients is very poor with metastases often present at the time of diagnosis. Despite the initial chemo-sensitivity the majority of the patients will relapse and die of their disease. Patient with Extensive Disease (ED) have a disappointing survival of 8−12 weeks without chemotherapy and 8−11 months after proper treatment. Irinotecan, a topoisomerase I inhibitor, has been reported as an active new agent in SCLC. In combination with cisplatin, it has showed superiority in response rates and progression free survival over the standard regimen of cisplatin and etoposide. We conducted a phase II study in order to evaluate the efficacy and safety of Carboplatin, Irinotecan and Etoposide (CIE) combination in extensive-disease SCLC (ED-SCLC)
Patients and Methods: Forty six chemo-naive patients with ED-SCLC and PS 0−2 were enrolled. Forty of them were men and 6 women. All of them were smokers and the median age was 59.6 years. We administered carboplatin AUC 5 on day 1, irinotecan 120/m2 on day 2 and etoposide 75 mg/m^2 on days 1, 2, 3 in a 21 days repeated cycles. The treatment was continued for up to 6 cycles. Response assessments were performed after cycles 3 and 6 and every 2 months subsequently. The patients were evaluated for response, survival and toxicity. Clinical (as site of metastasis) and laboratory (such as LDH) parameters were tested as prognostic factors for survival.
Results: Two hundred and two cycles were administered with an average of 4.5 cycle per patient. Overall response rate was 52.2% (partial and complete), mean overall survival was 16.3 months (CI: 95%: 13.0−19.7) and there was a 1 year survival rate of 43.47%. Patients with brain metastasis had worse prognosis (P:0.004).
The three drug regimen was well tolerated. Only 1 patient had diarrhea grade II, 6 had grade III/IV and 1 patient was referred with abdominal pain. One was presented with fatal thrombocytopenia while two toxic deaths were reported. Nine patients (19.5%) had neutropenia grade III/IV, without being fatal, and 3 were presented with grade III anemia which need blood transfusions.
Conclusion: CIE regimen is effective and well tolerated for the treatment of the poor prognosis group of ED-SCLC patients

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Preliminary findings of a phase I dose-escalation study of sunitinib in combination with gemcitabine plus cisplatin in advanced non-small cell lung cancer (NSCLC)

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Background: Sunitinib malate (SUTENT®; SU), is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs KIT, RET and FLT3, and is approved internationally for the treatment of advanced RCC and imatinib-resistant/-intolerant GIST. VEGFRs, which play a key role in angiogenesis, are overexpressed in NSCLC, and single-agent antitumor activity of sunitinib in advanced NSCLC patients (pts) has previously been demonstrated (11.1% response rate; Socinski, ESMO 2006). Preliminary findings of a phase I, dose-escalation study of SU in combination with gemcitabine (G) and cisplatin (C) are reported here.
Patients and Methods: Eligible pts have untreated, stage IIIB/IV NSCLC not amenable to curative treatment, ECOG PS $\leqslant$ 1 and adequate organ function. Pts receive SU (37.5 or 50 mg/d) on a repeated 2/1 schedule (2 wks on, 1 wk off treatment), plus G (1000 or 1250 mg/m^2 iv on days 1 and 8 of a 21 day cycle) and C (80 mg/m^2 iv on day 1 of each cycle). Evaluation of a continuous dosing (CD) schedule of SU is also planned. SU doses are escalated in serial pt cohorts to determine the primary endpoint – the maximum tolerated dose of SU for both dose schedules in this combination regimen. Secondary endpoints include the antitumor efficacy and pharmacokinetics of SU plus G and C.
Results: As of April 2007, 14 pts (9 males; mean age 60 years [range 48–68]) were treated with SU on the 2/1 schedule: 7 at 37.5 mg/d + G 1000 mg/m^2 + C 80 mg/m^2 (mean cycles started: 3, range 1–5); 7 at 50 mg/d + G 1000 mg/m^2 + C 80 mg/m^2 (mean cycles started: 4, range 1–6). No dose-limiting toxicities (DLTs) were observed with SU 37.5 mg/d. 2 pts receiving SU 50 mg/d experienced DLTs (1 dose-limiting neutropenia and infection, 1 neutropenia, infection and thrombocytopenia). Grade 3/4 neutropenia, thrombocytopenia and anemia occurred in 4, 3 and 2 pts receiving SU 37.5 mg/d, respectively, and in 5, 5 and 0 pts receiving SU 50 mg/d, respectively. In the 50 mg/d cohort, 3 pts achieved a partial response to treatment. No apparent drug–drug interactions were observed with SU in combination with G and C based on their systemic exposures in this study.
Conclusions: SU (37.5 mg/d) on a 2/1 schedule in combination with G (1000 mg/m^2) and C (80 mg/m^2) appears to have a favorable safety profile in pts with advanced NSCLC. Ongoing investigation will determine the safety of this combination regimen with G escalated to 1250 mg/m^2 and with SU administered on a CD schedule.

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An expanded access clinical program of erlotinib in patients (pts) with advanced stage IIIb/ IV non-small-cell lung cancer (NSCLC) – an update of a single institution experience

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Background: Erlotinib (Tarceva®) is a small molecule designed to target the human epidermal growth factor receptor 1 (EGF-HER1). It is designed to inhibit the tyrosine kinase activity of the EGF-HER1 signaling pathway inside the cell, which may block tumor cell growth. Erlotinib has proven activity in pretreated patients with advanced non-small-cell lung cancer (NSCLC) (F. Shepherd et al., N Engl J Med 2005; 353:123−32).
Methods: Pts with stage IIIB or IV NSCLC who have received up to two lines of standard systemic chemotherapy were planned to receive erlotinib 150 mg/day until disease progression or withdrawal. The primary end point of this EAP was to provide erlotinib to NSCLC patients and secondary to investigate best response, time to progression (TTP), overall survival and therapeutic safety in a broader pts population.
Results: 75 patients were enrolled from 01/05 to 10/05 in our department. All pts were treated with erlotinib. Pt characteristics: age: median 60 years (41−81); M/F 40/35; PS 0/1/2/3: 19/42/14/0; histopathology: adeno 42, squamous cell 17, bronchioalveolar (BAC) 8, large cell 4, others 4; smoking status: current or former/never: 14/61; prior chemotherapy line: median 2 (0−3).
At the time of the data cut-off, 1st March 2007, 68 patients had discontinued study treatment and 7 patients (9.3%) were still ongoing (non-progressive). The median time to progression is 2.8 months (95% CI: 2.0−3.8), and 20 pts have been treated for 24 weeks or longer with erlotinib. Two pts have been treated for 92 weeks. 24 patients (32%) were still alive at date of data cut-off.
Response assessment in 73 evaluable pts: PR (confirmed) 6 (8%), SD 42 (56%), PD 25 (33%), overall disease control rate (ODCR) 64%. Responses have been observed predominantly in adenocarcinoma (6).
As the most common adverse events rash I°/II°/III° (17/12/14) and diarrhea I°/II°/III° (7/5/1) were experienced. One additional patient developed nausea III° and another patient vomiting III°. No grade 4 events have been observed in the study population.
Conclusion: Erlotinib shows reproducible antitumor activity in patients with advanced stage IIIb or IV non-small-cell Lung Cancer after up to two prior chemotherapy regimens. Erlotinib was generally well tolerated, the main treatment-related adverse events were generally mild to moderate (rash and diarrhea). Selective patients experience longer survival duration over 18 months with this EGF-R inhibitor.
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Vandetanib in advanced non-small-cell lung cancer: an ongoing clinical evaluation programme

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Vandetanib (ZACTIMA™; ZD6474) is a once-daily oral anticancer drug in phase III clinical development in a broad population of patients with advanced NSCLC. Vandetanib targets VEGFR-dependent tumour angiogenesis and EGFR- and RET-dependent tumour growth and survival. Phase I evaluation in patients with advanced solid tumours showed vandetanib was generally well tolerated at daily oral doses of $\leqslant$300 mg. Common adverse events included rash, diarrhoea and asymptomatic QTc prolongation, all of which were controlled by standard management. A

series of randomized, double-blind phase II studies have investigated the efficacy of vandetanib in NSCLC. A two-part study compared vandetanib (300 mg) with gefitinib (IRESSA™; 250 mg) in 2nd/3rd-line NSCLC. The study achieved its primary efficacy objective: median progression-free survival (PFS) in part A was 11 weeks for vandetanib vs 8 weeks for gefitinib (HR = 0.69, 95% CI = 0.50–0.96; 1-sided P = 0.013). In 2nd-line NSCLC, vandetanib (100 or 300 mg) or placebo was assessed in combination with docetaxel. This study also achieved its primary objective, with vandetanib 100 mg + docetaxel demonstrating a significant prolongation of PFS vs docetaxel alone (HR = 0.64, 95% CI = 0.38–1.05; 1-sided P = 0.037). In 1st-line NSCLC, vandetanib (300 mg/day) ± carboplatin and paclitaxel (CP) was compared with CP + placebo. The primary objective was met, with vandetanib + CP prolonging PFS vs CP alone (HR = 0.76, 95% CI = 0.50–1.15; 1-sided P = 0.098): median PFS was 24 weeks (vandetanib + CP) and 23 weeks (CP). The vandetanib monotherapy arm was stopped early after a planned interim PFS analysis met the criterion for discontinuation (HR > 1.33 vs CP). In all three studies, no overall survival benefit with vandetanib was seen. However, the effect of vandetanib on survival (a secondary endpoint) may be confounded by the impact of post-progression therapies. The encouraging phase II data have led to the ongoing phase III evaluation of vandetanib in patients with advanced NSCLC, including squamous and non-squamous cell histology (Table).

An important question is whether predictive biomarkers can help to identify patient subgroups who will derive benefits from molecular targeted therapies? For example, several mutated protein kinases may be contributing to lung cancer, although mutations in each protein kinase are infrequent. The mutational spectra of protein kinases in most lung cancers are characterized by a high proportion of C:G > A:T transversions, compatible with the mutagenic effects of tobacco carcinogens.

Ongoing phase III studies of vandetanib in advanced NSCLC

	Vandetanib dose (mg/day)	Primary objective
Monotherapy		
Vandetanib vs placebo in patients previously treated with anti-EGFR therapy (6474IL0044)	300	Overall survival
Vandetanib vs erlotinib in refractory NSCLC (6474IL0057)	300	PFS
Combination regimens		
Vandetanib + docetaxel in 2nd-line NSCLC (6474IL0032)	100	PFS
Vandetanib + pemetrexed in 2nd-line NSCLC (6474IL0036)	100	PFS

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Safety of bevacizumab treatment in non-small cell lung cancer (NSCLC) subjects receiving full-dose anti-coagulation (FDAC) treated on protocol BO17704

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Background: Bevacizumab (Avastin®, B), in combination with cis-platin/gemcitabine prolongs progression-free survival in the first-line treatment of advanced NSCLC. Venous thrombosis necessitating FDAC is common in NSCLC. Due to concern about severe pulmonary haemorrhage (PH), there is limited experience with FDAC and B in the setting of NSCLC. We report here on the safety of B therapy in 53 NSCLC subjects treated with concomitant FDAC.

Methods: Subjects were treated on protocol BO17704, a randomised, double-blind phase III study of cisplatin/gemcitabine (CG) +/− B (7.5 or 15 mg/kg) for up to 6 cycles followed by B until disease progression, for first-line treatment of advanced/recurrent non-squamous NSCLC. FDAC was not permitted at study entry but was allowed for thrombotic events during study participation. Subjects on FDAC were identified by anticoagulant use and presence of a thrombotic adverse event (AE) after initiation of study treatment.

Results: Approximately 2/3 of FDAC subjects were treated with heparinoids; the remainder were treated with warfarin/warfarin derivatives.

Bleeding AEs	FDAC subjects (n = 86)			Non-anticoagulated subjects (n = 900)		
	Placebo + CG (n = 28) n/%	B 7.5 mg/kg + CG (n = 32) n/%	B 15 mg/kg + CG (n = 26) n/%	Placebo + CG (n = 299) n/%	B 7.5 mg/kg + CG (n = 298) n/%	B 15 mg/kg + CG (n = 303) n/%
All Gr 1–5	11 (39.3)	14 (43.8)	19 (73.1)	56 (18.7)	100 (33.6)	107 (35.3)
All Gr 3–5	1 (3.6)	2 (6.3)	2 (7.7)	5 (1.7)	12 (4.0)	13 (4.3)
PH Gr 1–5	3 (10.7)	2 (6.3)	5 (19.2)	14 (4.7)*	21 (7.0)	27* (8.9)
PH Gr 3–5	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)*	5 (1.7)	3* (1.0)

*Includes grade 5 PH (1 in placebo arm and 1 in B 15 mg/kg arm) determined by clinical review.

No bleeding events led to death in the FDAC population. There were no severe PH events in the FDAC population; all haemoptysis events were grade 1. Among subjects receiving FDAC, the majority of bleeding events were grade 1 epistaxis. All five grade 1−5 PH events in the B 15 mg/kg arm were grade 1 haemoptysis. In the FDAC population, there was one grade 4 CNS bleed (placebo arm) and one grade 2 CNS bleed (B 15 mg/kg arm).

Conclusions: There were no cases of severe PH in the FDAC population, although there were few events overall. As expected, bleeding rates are higher in the FDAC population, regardless of treatment.

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Determination of the prognostic value blood levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in advanced non-small cell lung cancer (NSCLC) patients

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Background: VEGF and bFGF are among the most important angiogenic factors. We have explored these angiogenesis mediators in plasma and its prognostic significance in advanced NSCLC.

Materials and Methods: Were enrolled 451 patients with advanced NSCLC, stages IIIB and IV and treated with cisplatin and docetaxel. Blood was collected before chemotherapy. Plasma VEGF and bFGF levels were assessed by commercial ELISA (sensitivity 5 pg/ml). In parallel plasma from 32 age and gender-matched controls was used.

Results: Median age was 61 years (35−82) and 84% were males. 99% had performance status 0−1. 84% were in stage IV and 16% in stage IIIB. The histological subtypes were: 32% squamous cell carcinoma, 50% adenocarcinoma, 14% anaplastic large cell, and 4% undifferentiated. 41% of the patients received second line chemotherapy. 1% achieved complete response (CR), 36% partial response (PR), 35% had stable disease (SD) and 28% progressive disease (PD). Patient's median plasma levels of VEGF (20 pg/ml, [6–203]) differ significantly (p = 0.04) from controls (14 pg/ml, [7−53]), but in contrast bFGF levels were not different, 14 pg/ml [5–960] vs 10 pg/ml [6–278] respectively. There were not differences in patients according to histology, site of metastasis and ECOG; however we could observe a tendency with stage for both factors: bFGF 9 pg/ml [5−24] in stage IIIB vs 15 pg/ml [6–960], p = 0.071 and VEGF 17 pg/ml [6–145] in IIIB vs 21 pg/ml [6–203] in IV, p = 0.086. It could not be observed any differences in response to therapy for both angiogenic factors; CR+PR patients presented median VEGF of 18 pg/ml [6−71] and bFGF 11 pg/ml [6–960] vs 20 pg/ml of VEGF [6–203] and 15 pg/ml of bFGF [5–395] in the SD+PD group. In the multivariate analysis we could not find that VEGF and bFGF plasma levels were predictors for time to progression (TTP) and overall survival (OS).

Conclusions: VEGF but not bFGF levels in patients are significantly higher in patients than in controls. In our cohort of patients with advanced NSCLC we have not found any relationship between serum VEGF and bFGF levels with stage, histology, response, site of metastasis, TTP and OS.