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

6610 POSTER

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.