

Published in final edited form as:

Lancet Oncol. 2010 July ; 11(7): 619–626. doi:10.1016/S1470-2045(10)70132-7.

Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial

Prof Roy S Herbst, MD, Yan Sun, MD, Wilfried E E Eberhardt, MD, Paul Germonpré, MD, Prof Nagahiro Saijo, MD, Caicun Zhou, MD, Jie Wang, MD, Longyun Li, MD, Fairouz Kabbinavar, MD, Yukito Ichinose, MD, Shukui Qin, MD, Li Zhang, MD, Bonne Biesma, MD, John V Heymach, MD, Peter Langmuir, MD, Sarah J Kennedy, MSc, Hiroomi Tada, MD, and Prof Bruce E Johnson, MD

University of Texas MD Anderson Cancer Center, Houston, TX, USA (Prof R S Herbst MD, J V Heymach MD); Cancer Hospital, Beijing, China (Y Sun MD); Department of Medicine/Cancer Research, West German Tumor Centre, University Duisburg-Essen, Essen, Germany (W E E Eberhardt MD); Antwerp University Hospital, Antwerp, Belgium (P Germonpré MD); Kinki University School of Medicine, Osaka, Japan (Prof N Saijo MD); Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China (C Zhou MD); Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing, China (J Wang MD); Peking Union Medical College, Beijing, China (L Li MD); UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA (F Kabbinavar MD); National Kyusyu Cancer Center, Fukuoka, Japan (Y Ichinose MD); Nanjing Bayi Hospital, Nanjing, China (S Qin MD); Sun Yat-Sen University Cancer Center, Guangzhou, China (L Zhang MD); Afdeling Longziekten, Jeroen Bosch Ziekenhuis, Hertogenbosch, Netherlands (B Biesma MD); AstraZeneca, Wilmington, DE, USA (P Langmuir MD, H Tada MD); AstraZeneca, Macclesfield, UK, USA (S J Kennedy MSc); Dana-Farber Cancer Institute, Boston, MA, USA (Prof B E Johnson MD)

Summary

Background—Vandetanib is a once-daily oral inhibitor of vascular endothelial growth factor receptor, epidermal growth factor receptor, and rearranged during transfection (RET) tyrosine kinases. In a randomised phase 2 study in patients with previously treated non-small-cell lung cancer (NSCLC), adding vandetanib 100 mg to docetaxel significantly improved progression-free survival (PFS) compared with docetaxel alone, including a longer PFS in women. These results supported investigation of the combination in this larger, definitive phase 3 trial (ZODIAC).

Correspondence to: Prof Roy S Herbst, Department of Thoracic/Head and Neck Medical, Oncology, Department of Cancer, Biology, University of Texas MD, Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 432, Houston, TX 77030-4009, USA, rherbst@mdanderson.org.

Contributors

RSH, BEJ, and PL were involved in the conception and design of the study. RSH, BB, CZ, FK, BEJ, LL, PG, SQ, WEEE, YS, YI, and LZ were involved in the provision of study material or patients, or data acquisition. HT, JVH, and SJK were involved in data analysis and interpretation. RSH, BB, CZ, FK, HT, JVH, BEJ, LL, NS, PG, PL, SQ, SJK, WEEE, YS, and LZ were involved in writing and critical review of the manuscript. All authors approved the final version. A full list of study investigators can be found in the webappendix.

Conflicts of interest

RSH received fees for consultancy (AstraZeneca steering committee) and grant support from AstraZeneca. WEEE received fees for an advisory board (ZODIAC steering committee) and a speaker's bureau from AstraZeneca. PG received fees for an advisory board (ZODIAC steering committee) and accommodation expenses from AstraZeneca. YI received fees for honoraria from AstraZeneca. LZ received fees from AstraZeneca for presentation of data from this study at a regional meeting. JVH received fees for consultancy, grants, and honoraria from AstraZeneca. PL, SJK, and HT are employees of AstraZeneca and PL has stock in the company. BEJ received grant support, consultancy and honoraria fees (ZODIAC steering committee), and travel support from AstraZeneca. All other authors declared no conflicts of interest.

Methods—Between May, 2006, and April, 2008, patients with locally advanced or metastatic (stage IIIB–IV) NSCLC after progression following first-line chemotherapy were randomly assigned 1:1 through a third-party interactive voice system to receive vandetanib (100 mg/day) plus docetaxel (75 mg/m² IV every 21 days; maximum six cycles) or placebo plus docetaxel. The primary objective was comparison of PFS between the two groups in the intention-to-treat population. Women were a coprimary analysis population. This study has been completed and is registered with ClinicalTrials.gov, number NCT00312377.

Findings—1391 patients received vandetanib plus docetaxel (n=694 [197 women]) or placebo plus docetaxel (n=697 [224 women]). Vandetanib plus docetaxel led to a significant improvement in PFS versus docetaxel alone (hazard ratio [HR] 0.79, 95% CI 0.70–0.90; p<0.0001); median PFS was 4.0 months in the vandetanib group versus 3.2 months in placebo group. A similar improvement in PFS with vandetanib plus docetaxel versus placebo plus docetaxel was seen in women (HR 0.79, 0.62–1.00, p=0.024); median PFS was 4.6 months in the vandetanib group versus 4.2 months in the placebo group. Among grade 3 or higher adverse events, rash (63/689 [9%] vs 7/690 [1%]), neutropenia (199/689 [29%] vs 164/690 [24%]), and febrile neutropenia (61/689 [9%] vs 48/690 [7%]) were more common with vandetanib plus docetaxel than with placebo plus docetaxel. The most common serious adverse event was febrile neutropenia (46/689 [7%] in the vandetanib group vs 38/690 [6%] in the placebo group).

Interpretation—The addition of vandetanib to docetaxel provides a significant improvement in PFS in patients with advanced NSCLC after progression following first-line therapy.

Funding—AstraZeneca.

Introduction

Non-small-cell lung cancer (NSCLC) is a major cause of cancer-related death and most patients are diagnosed with NSCLC at an advanced stage of disease.^{1,2} Many patients initially achieve clinical remission or disease stabilisation with first-line therapy, but nearly all experience disease progression and eventually die from advanced NSCLC. Several drugs are approved as second-line treatments for advanced NSCLC, including docetaxel,^{3,4} pemetrexed,⁵ erlotinib,⁶ and gefitinib;⁷ however, none have shown a clear advantage in this setting. One strategy to improve efficacy and alleviate symptom burden, without increasing toxicity, is to combine chemotherapeutics with drugs that selectively target signalling pathways associated with lung-cancer progression.

Vandetanib (AstraZeneca, Macclesfield, UK) is a once-daily oral anticancer drug that targets vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) signalling.^{8,9} Vandetanib is also a potent inhibitor of RET tyrosine kinase, an important growth driver in some thyroid cancers¹⁰ and possibly other cancers.¹¹ The rationale for simultaneous targeting of VEGFR and EGFR with vandetanib is supported by evidence from clinically relevant xenograft models of human NSCLC,¹² which showed that vandetanib could abrogate primary and acquired resistance to EGFR tyrosine-kinase inhibitors (TKIs). In some of these preclinical models, resistance to EGFR inhibitors was associated with increased expression of tumour-derived and host-derived VEGF. Both the VEGFR and EGFR signalling pathways are established therapeutic targets in patients with advanced NSCLC: bevacizumab, an anti-VEGF monoclonal antibody, prolonged survival when added to paclitaxel and carboplatin in previously untreated non-squamous advanced NSCLC¹³ (bevacizumab is not indicated in patients with squamous histology because of the risk of life-threatening haemoptysis), and the EGFR inhibitors gefitinib and erlotinib have shown single-agent activity in previously treated advanced NSCLC.^{6,7}

Phase 2 assessment of vandetanib has shown antitumour activity in advanced, previously treated NSCLC^{14,15} and in hereditary medullary thyroid cancer.¹⁶ In patients with previously treated NSCLC, vandetanib 100 mg/day plus docetaxel improved progression-free survival (PFS; hazard ratio [HR] 0.64) and objective response rate (ORR) versus docetaxel alone.¹⁴ Additionally, exploratory subgroup analyses showed a greater PFS benefit in women (HR 0.31) than in men (HR 0.87) with vandetanib 100 mg plus docetaxel versus docetaxel alone. The trial also showed that vandetanib 100 mg plus docetaxel resulted in a longer PFS and was better tolerated than vandetanib 300 mg plus docetaxel. Overall, these phase 2 results provided the rationale for further assessment of vandetanib 100 mg/day plus docetaxel in the randomised, placebo-controlled, phase 3 study (Zactima in combination with Docetaxel in non-small cell lung Cancer [ZODIAC]) reported here.

Methods

Study design and patients

ZODIAC was a multinational, randomised, double-blind, phase 3 study of vandetanib plus docetaxel (Sanofi-Aventis, Paris, France) versus placebo plus docetaxel in patients with locally advanced or metastatic NSCLC after progression following platinum-based first-line chemotherapy. Docetaxel was chosen for this study because the recent approval and increasing use of pemetrexed as first-line therapy in NSCLC suggests a continuing role for docetaxel as second-line therapy.

Eligibility criteria included age 18 years or older; histological or cytological confirmation of locally advanced or metastatic stage IIIB–IV NSCLC after failure of first-line platinum-based therapy; WHO performance status of 0 or 1; measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST); no previous therapy with docetaxel or a VEGFR TKI; and adequate cardiac, haematopoietic, hepatic, and renal function. Patients with squamous-cell histology were eligible, and brain metastases were permitted if treated at least 4 weeks before study entry and clinically stable without steroids for 10 days. Previous treatment with bevacizumab or paclitaxel was also permitted.

The trial was approved by the institutional review boards or ethical committees at each centre, and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca Bioethics policy. All patients provided written informed consent.

Randomisation and masking

A standard computerised randomisation scheme was used to randomly assign treatment to patients (1:1). Randomisation numbers were allocated to centres in balanced blocks. The block size was such that the randomisation scheme was effectively stratified by centre. Eligible patients were randomised strictly sequentially. After a patient was screened for eligibility, the investigator contacted the centralised registration/randomisation centre (CR/RC) by telephone and an interactive voice response system (IVRS) was used to assign a unique randomisation code to each patient and allocate blinded randomised therapy. Medication was labelled using a unique material pack code linked to the randomisation scheme, and was assigned by the CR/RC to be dispensed to each patient at each visit. The active and placebo tablets were identical and were presented in the same packaging. Each patient's randomisation code break was available to the local investigator through the IVRS. The treatment code was to be broken only in medical emergencies; otherwise, codes were not broken for the planned analyses until all decisions on the evaluability of data from each patient had been made and documented. This masking was maintained for AstraZeneca personnel responsible for analysis and interpretation of results at the study's conclusion.

Procedures

Patients were randomly assigned to receive docetaxel (75 mg/m² in a 1-h intravenous infusion every 3 weeks; maximum six cycles) in combination with vandetanib (100 mg/day orally) or placebo until disease progression, unacceptable toxicity, or withdrawal of consent. Consistent with Japanese prescribing information, the docetaxel dose in Japan was 60 mg/m².

The primary objective was to assess whether vandetanib plus docetaxel prolonged PFS compared with placebo plus docetaxel. PFS was selected as the primary endpoint to provide a direct measurement of the effect of study treatment on the tumour, since, unlike overall survival, PFS is not potentially confounded by the use of post-progression therapies. Secondary endpoints included assessments of overall survival, ORR (complete+partial responses), disease control rate (complete+partial responses+stable disease ≥ 6 weeks), time to deterioration of disease-related symptoms, and safety.

Objective tumour response was assessed radiologically by the local investigators according to RECIST 1.0, with assessments done at baseline and every 6 weeks until progression. There was no independent blinded review of radiological assessments, which is consistent with other studies using PFS as the primary endpoint.^{17,18} Although the absence of independent radiological assessment is a potential limitation of the study, it was considered sufficient that the study was double-blind and randomised, and the common side-effects predicted for the drug combination (rash and diarrhoea) are similar to those seen with docetaxel alone.

PFS was defined as the time from randomisation to the earliest occurrence of disease progression or death from any cause, provided death was within 3 months of the last evaluable assessment. Patients who had not progressed or died at the time of statistical analysis were censored at the time of their latest evaluable RECIST assessment. Although PFS is often defined as the time from randomisation to progression (or death by any cause in the absence of progression), a 3-month limit was adopted for the Food and Drug Administration (FDA)-reviewed study, to minimise artificial prolongation of PFS.

Overall survival was calculated from the date of randomisation to the date of death by any cause; patients who had not died at the time of analysis were censored at the time they were last known to be alive. An unplanned overall survival update was also done in accordance with a request from the FDA, and the results of this analysis are reported for completeness. No efficacy endpoints other than survival were updated at this time.

Symptoms were assessed using the seven-item Lung Cancer Subscale (LCS) derived from the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire that has been previously validated in patients with lung cancer.¹⁹ The FACT-L questionnaire was given to patients at baseline and every 3 weeks thereafter, until 30 days after progression or discontinuation of treatment. The LCS consists of three items relating to breathing or dyspnoea and one item each relating to cough, weight loss, appetite, and cognition. Each item is rated on a five-point scale (0 [worst] to 4 [best]), with a total score ranging from 0 (most symptomatic) to 28 (asymptomatic). Deterioration was predefined as an adverse change of three points or more from baseline, with no improvement in the next 21 days, which has been shown to be a clinically meaningful change in patients with advanced NSCLC.²⁰ Time to deterioration of symptoms (TDS) was the interval from date of randomisation to first assessment of symptom deterioration (as defined above). If deterioration was not observed at the time of analysis, TDS was censored at the time of the last evaluable LCS assessment.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 3.0). Prespecified groups of preferred terms were identified as being of interest, based on pharmacological class or previous studies with vandetanib. Scheduled 12-lead ECGs were done during screening, at 1, 3, 6, and 12 weeks after starting randomised treatment and every 3 months thereafter, and at the end of study. The QTc interval was assessed centrally, and prolongation was defined as previously described.¹⁶ Management of adverse events generally consisted of dose interruption followed by dose reduction as necessary.

Statistical analysis

The study had two coprimary analysis populations: all randomised patients (intention-to-treat [ITT]) and all randomised female patients. The conventional 5% significance level was therefore adjusted to 2.5% for all analyses, and further adjusted to 2.42% for PFS and 2.48% for overall survival to allow a single interim analysis. P values are two-sided. The study was designed to have greater than 90% power to detect a 25% prolongation of PFS (HR <0.80). Assuming a median PFS of 3 months for docetaxel alone, a sample size of 1380 patients was estimated to achieve 1176 progression events, with accrual over 19 months and a minimum follow-up of 3 months.

PFS, overall survival, and TDS were analysed using the log-rank test (unadjusted model with treatment factor only). A secondary analysis of PFS and overall survival was done using Cox's proportional-hazards regression model that allowed for the effect of treatment and included terms for tumour stage, number of organs involved, previous bevacizumab failures, histology, smoking history, sex, ethnic origin, and plasma and tumour biomarker status. The ORR and disease control rate were analysed using logistical regression. Patients were stratified only by centre.

Patients of east Asian origin have previously been shown to derive differential benefit from anti-EGFR treatment.²¹ Interaction tests were therefore done before the main study analyses to determine if the treatment effect in Japan or China differed from that in all other countries. The interaction test was done for PFS and OS at a two-sided, 10% significance level. All statistical analyses were done using SAS version 9.1. This study is registered with ClinicalTrials.gov, number NCT00312377.

Role of the funding source

The corresponding author designed the trial in collaboration with the study sponsor, and the steering committee met nine times during the trial to supervise the conduct of the study. The sponsor provided funding and organisational support, collected the data, and undertook the analyses. The report was written by the senior investigators, who had unrestricted access to the study data and gave assurance for the accuracy and completeness of the reported analyses. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between May, 2006, and April, 2008, 1391 patients recruited from 198 centres in 25 countries were randomly assigned to receive vandetanib plus docetaxel (n=694) or placebo plus docetaxel (n=697; figure 1). Patient characteristics and baseline demographics were similar in both treatment groups (table 1). At data cut-off (Aug 22, 2008), 1205 patients (87%) had progressed, 814 (59%) had died, and the median potential duration of follow-up was 12.8 months. The median number of docetaxel cycles in each group was four (range 1–6). The total median duration of exposure to vandetanib or placebo was 12.1 weeks (range

0.1–103.9) and 13.0 weeks (range 0.1–84.9), respectively. Dose intensity of docetaxel was not compromised by the addition of vandetanib, with a median of 98.1% of the planned dose being received in the vandetanib group versus 98.4% in the placebo group. The numbers and types of subsequent anticancer therapies were well balanced between groups, with 51% (351) patients in the vandetanib group and 55% (387) in the placebo group receiving at least one post-progression therapy. Before the main study analyses, formal assessment of whether treatment effects (PFS and overall survival) in Japan or China differed from all other countries did not show significant qualitative interaction—ie, no evidence of treatment effects in opposite directions. The main study analyses therefore included patients from Japan and China.

Patients randomly assigned to receive vandetanib plus docetaxel showed a significant improvement in PFS versus those randomly assigned to receive placebo plus docetaxel for the overall population (HR 0.79, 97.58% CI 0.70–0.90; $p < 0.0001$; figure 2A); median PFS was 4.0 months in the vandetanib group versus 3.2 months in the placebo group. At 6 months, 28% of patients in the vandetanib group and 22% in the placebo group were progression-free. A similar improvement in PFS with vandetanib plus docetaxel versus placebo plus docetaxel was observed in women (HR 0.79; 0.62–1.00; $p = 0.024$); median PFS was 4.6 months in the vandetanib group versus 4.2 months in the placebo group.

The addition of vandetanib to docetaxel also resulted in a significant improvement in ORR (17% [120 patients] vs 10% [71 patients], $p = 0.0001$): all were partial responses in the vandetanib group, with six complete responses and 65 partial responses in the placebo group. The disease control rate was comparable in both groups: 60% (413 patients) with vandetanib plus docetaxel versus 55% (380 patients) with placebo plus docetaxel ($p = 0.06$). At data cut-off for PFS analysis (814/1391 [59%] of patients dead), there was no significant difference between treatment groups for the secondary endpoint of overall survival (HR 0.91, 97.52% CI 0.78–1.07; $p = 0.196$; figure 2B); similar results were observed in women (HR 0.96, 0.71–1.30; $p = 0.759$). The proportion of patients alive at 1 year was 44.7% in the vandetanib group versus 41.2% in the placebo group. The results of preplanned exploratory subgroup analyses for PFS and overall survival were generally consistent with the results seen in all patients, including those with squamous-cell histology (figure 3).

Overall compliance with the FACT-L questionnaire, calculated as patients with a baseline evaluable assessment and at least one follow-up evaluable assessment, was 72% (503 patients) in the vandetanib group and 74% (515 patients) in the placebo group. TDS was delayed in the vandetanib group compared with in the placebo group (HR 0.77, 97.5% CI 0.65–0.92; $p = 0.0008$; FACT-L LCS; figure 4). Median TDS was 3.5 months in the vandetanib group versus 2.7 months in the placebo group. At 6 months, 34% of patients in the vandetanib group and 26% in the placebo group had not experienced deterioration of symptoms.

At the time of overall survival follow-up analysis (September, 2009), 1075 patients had died: 538 (78%) in the vandetanib group and 537 (77%) in the placebo group. There was no significant difference in overall survival (HR 0.95, 95% CI 0.84–1.07; $p = 0.371$); median overall survival was 10.3 months in the vandetanib group and 9.9 months in the placebo group. The overall survival subgroup results were consistent with those from the August data cut-off (data not shown).

Adverse events (all grades) occurring more frequently in the vandetanib group included diarrhoea, rash, and neutropenia (table 2). Nausea, vomiting, and anaemia occurred less frequently in the vandetanib group (table 2). Protocol-defined QTc prolongation occurred in 1.9% (13/689) of patients receiving vandetanib (vs none in the placebo group); all events

were asymptomatic and resolved with dose interruption, reduction, or discontinuation. Overall, 22.2% (153/689) of patients in the vandetanib group and 11.0% (76/690) in the placebo group had an adverse event that led to discontinuation of vandetanib or placebo. The proportion of patients requiring dose interruption or reduction of vandetanib or placebo was higher in the vandetanib group (23% [157/689]) than in the placebo group (14% [97/690]). The incidence of hypertension was 6% (41/689; 35 grade 1 or 2, six grade 3) with vandetanib plus docetaxel and 2% (12/690; 11 grade 1 or 2, one grade 3) with placebo plus docetaxel. The incidence of haemorrhage was 17% (116/689) in the vandetanib group versus 16% (112/690) in the placebo group; the incidence of venous thrombotic or embolic events was 2% (14/689) in the vandetanib group versus 4% [27/690] in the placebo group. The incidence of haemoptysis was 6% (40/689) in the vandetanib group versus 7% (50/690) in the placebo group, with one fatal case in each group.

Among grade 3 or higher adverse events, rash, neutropenia, and febrile neutropenia occurred more frequently in the vandetanib group than in the docetaxel group (table 2). More patients required dose interruption or reduction in the vandetanib group than in the placebo group (23% [157/689] vs 14% [97/690]), which was mainly due to the higher incidence of rash leading to dose interruption or reduction (11% [73/689] vs 1% [5/690]). Serious adverse events leading to death occurred in 42 of 689 (6%) of patients in the vandetanib group and 38 of 690 (6%) in the placebo group. The most common serious adverse event was febrile neutropenia (7% [46/689] in the vandetanib group and 6% [38/690] in the placebo group). Consistent with the natural history for patients with lung cancer, the most commonly reported serious adverse events that led to death in either group were pneumonia (n=11), respiratory failure (n=10), and dyspnoea (n=5). Three deaths were attributed to interstitial lung disease, including two patients from Japan. All three patients had received vandetanib plus docetaxel. There were two deaths from skin reactions in the vandetanib group (Stevens–Johnson syndrome and toxic skin eruption), compared with none in the placebo group.

Discussion

In this randomised, double-blind, international phase 3 study, vandetanib in combination with docetaxel chemotherapy significantly prolonged the time to disease progression, compared with placebo plus docetaxel, for patients with advanced metastatic NSCLC in the second-line setting. Patients in the vandetanib plus docetaxel group also had a higher ORR and longer time to deterioration in lung-cancer symptoms than did those in the placebo group.

The study was representative of the patient population receiving second-line treatment for NSCLC, and docetaxel exposure (median four cycles) was generally consistent with standard clinical practice and with previous second-line trials of the drug at 75 mg/m².^{2–5} However, in the present study, the median overall survival of 10 months for patients receiving placebo plus docetaxel is longer than that reported in the earlier studies (range 5.7–7.9 months). This difference might be explained by differences in the availability or use of first-line and post-progression therapies, as well as general improvements in standards of care over time. Unknown differences in the baseline characteristics of patients in the present study might also be a factor.

It is unclear why the PFS advantage for patients receiving vandetanib did not translate into an improvement in overall survival. However, differences between treatment groups in the use of, and response to, post-progression therapies might have confounded the overall survival outcome. About 50% of patients received post-progression therapy; although the number of patients and type of therapy received was balanced across groups, it cannot be

excluded that differences in response to post-progression therapy could have contributed to the results.

Despite the absence of an overall benefit with vandetanib plus docetaxel, the longer PFS in the group that received this combination, relative to those who received placebo plus docetaxel, was associated with a significant delay in time to deterioration of common lung-cancer symptoms; the magnitude of benefit (in terms of HR and median prolongation) favouring vandetanib plus docetaxel was very similar for PFS and TDS. This improvement in symptom relief experienced by patients receiving vandetanib raises the possibility that patients with advanced NSCLC can live with fewer symptoms (and therefore fewer interventions) for a longer period of time. Since progressive disease is generally associated with a worsening in disease-related symptoms, the results of the present study suggest that slowing disease progression also slowed symptom progression, leading to an important palliative benefit. The lower rate of treatment-related toxic effects with vandetanib, such as nausea, vomiting, and anaemia, might also be a factor, although it is not clear how a decrease in these effects relates to delay in the time to worsening of lung-cancer symptoms measured by the LCS. Symptoms measured by the LCS correlate with PFS and ORR, as shown in three phase 3 studies of gefitinib (ISEL, INTEREST, and iPASS).^{7,17,21} Previous studies by Cella and colleagues²⁰ and others²² have shown that an increase of 2–3 points represents an improvement in symptoms and a decrease of 2–3 points represents a deterioration of symptoms. Cella and colleagues²⁰ showed a greater deterioration of symptoms in early progressors than in late progressors, with a 3·1-point difference in LCS mean change scores between these groups and a 3-point change in symptoms correlating with time to progression and overall survival.

Predefined subgroup analyses for patient and clinical characteristics did not show clear evidence of a significant differential benefit for PFS or overall survival. This included women, who were a coprimary analysis population based on preliminary evidence from a phase 2 study that suggested that women receiving vandetanib plus docetaxel (versus docetaxel) experienced a greater PFS benefit than men.¹⁴ These findings were not confirmed in the present study, underscoring the importance of confirming exploratory findings in a larger definitive study. Subgroup analysis of tumour and circulating biomarker data, including analysis of *EGFR* mutation status, *EGFR* expression, and *EGFR* amplification by fluorescence in-situ hybridisation, is ongoing. There was also no suggestion of a disadvantage in efficacy for the small number of patients who had previously received bevacizumab.

Patients receiving vandetanib did not show an increased incidence of haemoptysis, suggesting that vandetanib, unlike bevacizumab,²³ can be administered safely to all histological NSCLC subtypes. Patients receiving vandetanib had a lower incidence of some toxic effects (nausea, vomiting, and anaemia) commonly associated with chemotherapy treatment. Although there is no obvious explanation, a similar pattern was observed in the ZEAL phase 3 study, which investigated vandetanib plus pemetrexed in previously treated NSCLC.²⁴ The lower incidence of nausea or vomiting did not seem to be due to increased antiemetic use or reduced chemotherapy exposure with vandetanib. The increased frequency of hypertension and rash or diarrhoea in the vandetanib group is consistent with pharmacodynamic inhibition of VEGFR and EGFR signalling pathways, respectively. Four previous phase 3 studies in advanced NSCLC did not find an efficacy benefit when the EGFR TKIs erlotinib or gefitinib were added to standard first-line doublet chemotherapy.^{25–28} More recently, the FLEX study showed that addition of the anti-EGFR monoclonal antibody cetuximab to platinum-based chemotherapy can improve survival in the first-line setting.²⁹ In the present study, vandetanib provided additional antitumour activity when combined with chemotherapy, although it remains to be determined whether

this occurred despite the anti-EGFR activity of vandetanib, or whether the combined anti-VEGFR and anti-EGFR effects of the drug are contributing to the overall efficacy when used with docetaxel.

The results of this large phase 3 study are generally consistent with those obtained in the smaller ZEAL phase 3 study.²⁴ Significant PFS prolongation was not observed in the ZEAL study (HR 0.86, 97.58% CI 0.69–1.06; $p=0.108$), but the vandetanib plus chemotherapy group in both trials showed a significantly higher ORR and improved symptom control versus the placebo group, as well as an acceptable safety profile. The antitumour activity of vandetanib in advanced NSCLC is also supported by the ZEST monotherapy phase 3 study versus erlotinib, which did not find a PFS benefit with vandetanib, but showed comparable efficacy (including a 12% ORR).³⁰

The ZODIAC study shows that adding vandetanib to docetaxel in patients with previously treated advanced NSCLC (all histologies) can slow disease progression, and this is associated with better control of the symptoms caused by lung cancer. To the best of our knowledge, vandetanib is the first oral targeted therapy in phase 3 trials to show significant evidence of additional efficacy when added to standard chemotherapy, in patients with previously treated NSCLC.

Acknowledgments

We acknowledge the valuable contribution of the independent data monitoring committee (Malcolm Ranson, Philip Bonomi, Stuart Pocock, Tomohide Tamura, Pan-Chyr Yang) and the independent statistical data analysis centre (Duolao Wang) to the oversight and conduct of this study. This study was supported financially by AstraZeneca. We thank John Matthew of Mudskipper Bioscience for editorial assistance funded by AstraZeneca.

References

1. WHO. Cancer factsheet. 2009. <http://www.who.int/mediacentre/factsheets/fs297/en/> (accessed)
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009; 59:225–49. [PubMed: 19474385]
3. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000; 18:2095–103. [PubMed: 10811675]
4. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000; 18:2354–62. [PubMed: 10856094]
5. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004; 22:1589–97. [PubMed: 15117980]
6. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005; 353:123–32. [PubMed: 16014882]
7. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*. 2008; 372:1809–18. [PubMed: 19027483]
8. Herbst RS, Heymach JV, O'Reilly MS, Onn A, Ryan AJ. Vandetanib (ZD6474): an orally available receptor tyrosine kinase inhibitor that selectively targets pathways critical for tumor growth and angiogenesis. *Expert Opin Investig Drugs*. 2007; 16:239–49.
9. Wedge SR, Ogilvie DJ, Dukes M, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res*. 2002; 62:4645–55. [PubMed: 12183421]

10. Carlomagno F, Vitagliano D, Guida T, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res.* 2002; 62:7284–90. [PubMed: 12499271]
11. Beaudry P, Nilsson M, Rieth M, et al. Potent antitumor effects of ZD6474 on neuroblastoma via dual targeting of tumor cells and tumor endothelium. *Mol Cancer Ther.* 2008; 7:418–24. [PubMed: 18245671]
12. Naumov GN, Nilsson MB, Cascone T, et al. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. *Clin Cancer Res.* 2009; 15:3484–94. [PubMed: 19447865]
13. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006; 355:2542–50. [PubMed: 17167137]
14. Heymach JV, Johnson BE, Prager D, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non-small-cell lung cancer. *J Clin Oncol.* 2007; 25:4270–77. [PubMed: 17878479]
15. Natale RB, Bodkin D, Govindan R, et al. Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: results from a two-part, double-blind, randomized phase II study. *J Clin Oncol.* 2009; 27:2523–29. [PubMed: 19332730]
16. Wells SA Jr, Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol.* 2010; 28:767–72. [PubMed: 20065189]
17. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009; 361:947–57. [PubMed: 19692680]
18. Reck M, Von PJ, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol.* 2009; 27:1227–34. [PubMed: 19188680]
19. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer.* 1995; 12:199–220. [PubMed: 7655830]
20. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol.* 2002; 55:285–95. [PubMed: 11864800]
21. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet.* 2005; 366:1527–37. [PubMed: 16257339]
22. Butt Z, Webster K, Eisenstein AR, et al. Quality of life in lung cancer: the validity and cross-cultural applicability of the Functional Assessment Of Cancer Therapy-Lung scale. *Hematol Oncol Clin North Am.* 2005; 19:389–420. [PubMed: 15833412]
23. Genentech. AVASTATIN: highlights of prescribing information. <http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf> (accessed)
24. De Boer R, Arrieta Ó, Gottfried M, et al. Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZEAL). *Proc Am Soc Clin Oncol.* 2009; 27:abst 8010.
25. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol.* 2007; 25:1545–52. [PubMed: 17442998]
26. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol.* 2004; 22:777–84. [PubMed: 14990632]
27. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol.* 2004; 22:785–94. [PubMed: 14990633]

28. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2005; 23:5892–99. [PubMed: 16043829]
29. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet*. 2009; 373:1525–31. [PubMed: 19410716]
30. Natale RB, Thongprasert S, Greco FA, et al. Vandetanib versus erlotinib in patients with advanced non-small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: a randomized, double-blind phase III trial (ZEST). *Proc Am Soc Clin Oncol*. 2009; 27:abst 8009.

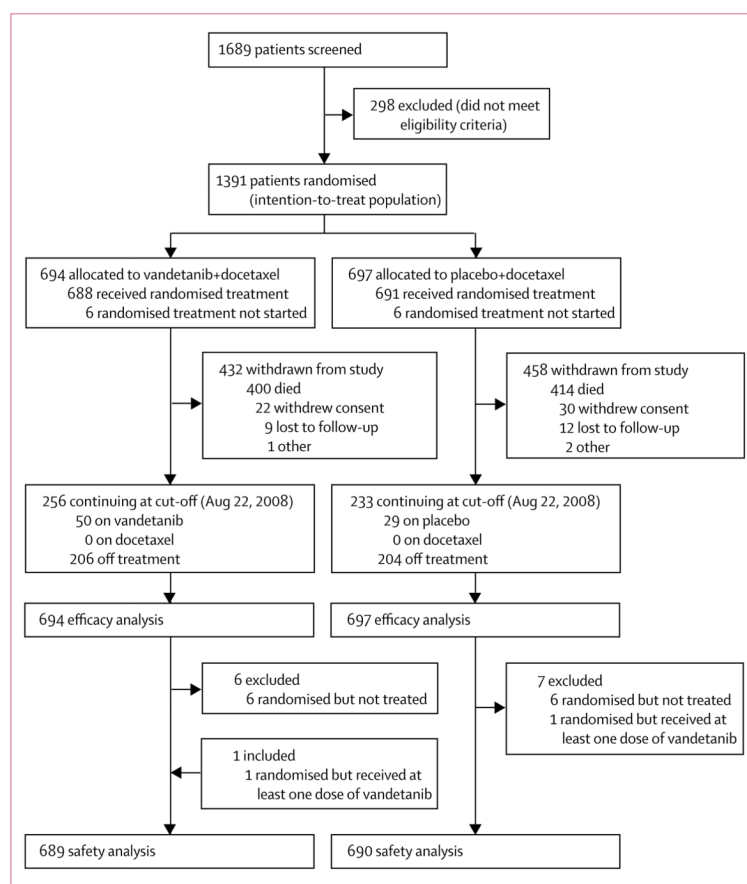


Figure 1.
Trial profile

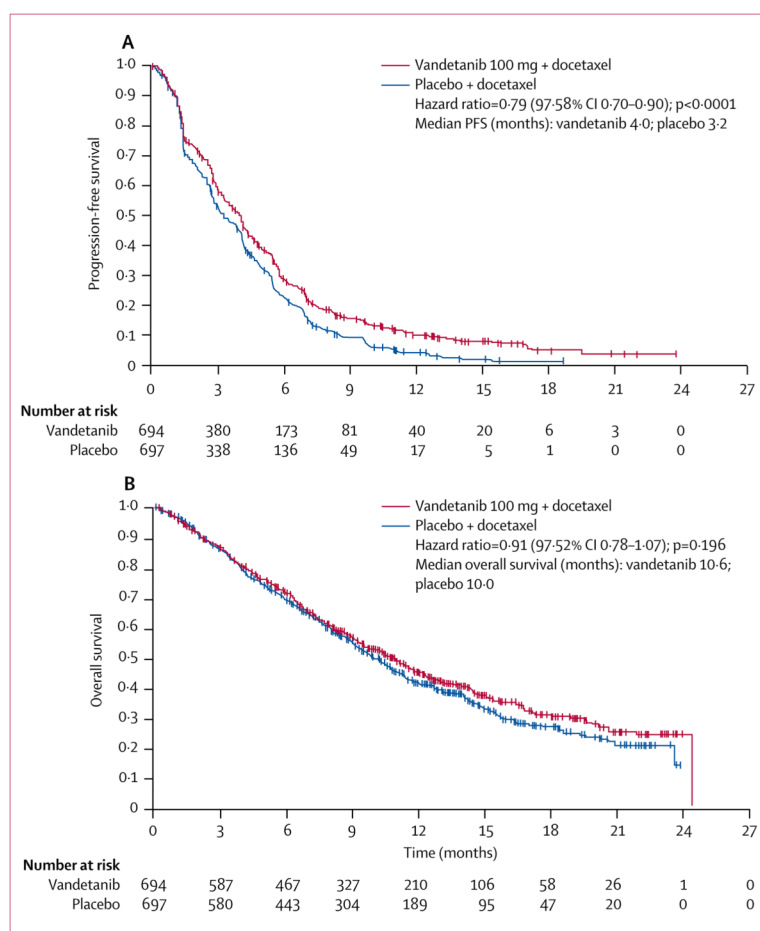


Figure 2. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in the intention-to-treat population (all randomised patients)

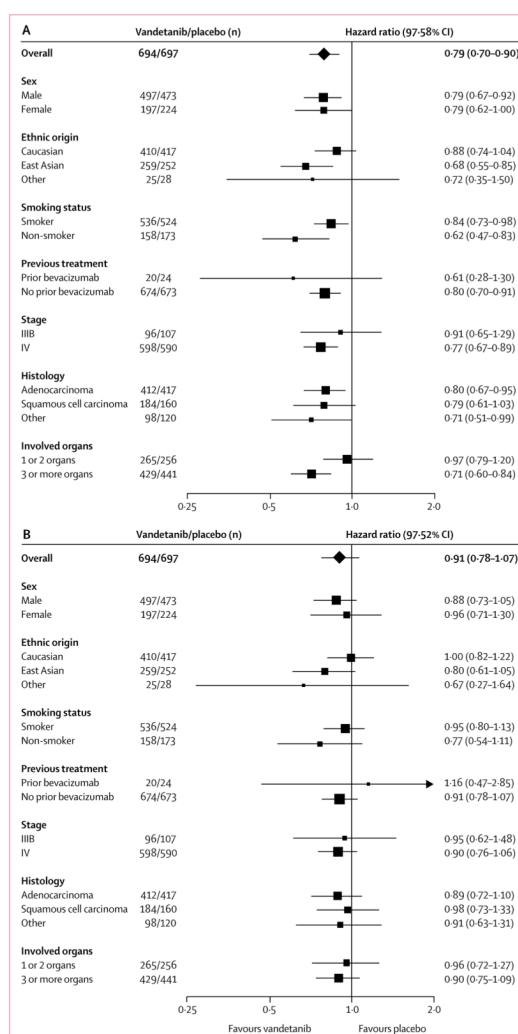


Figure 3. Hazard ratios for progression-free survival (A) and overall survival (B) by patient and clinical characteristics in the intention-to-treat population (all randomised patients)
Analyses were done using a log-rank test with treatment as the only factor.

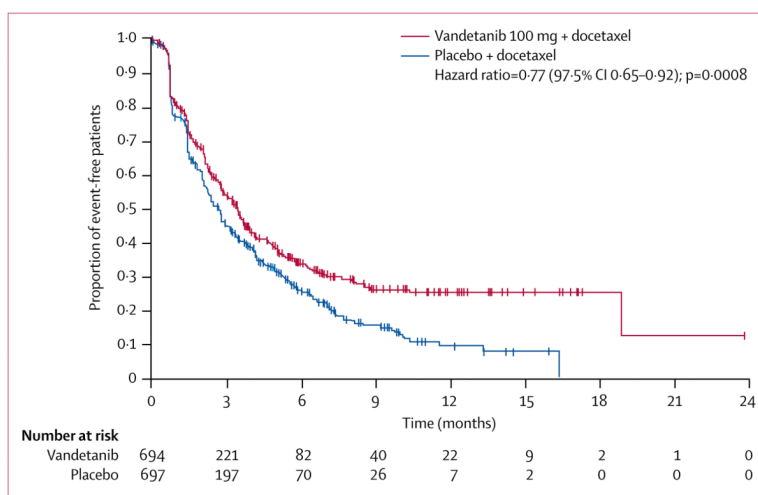


Figure 4. Kaplan-Meier estimates of time to deterioration in symptoms (FACT-L, Lung Cancer Subscale) in the intention-to-treat population (all randomised patients)
FACT-L=Functional Assessment of Cancer Therapy-Lung questionnaire

Table 1

Patient demographics and baseline characteristics in the ITT population (all randomised patients)

	Vandetanib+docetaxel (n=694)	Placebo+docetaxel (n=697)
Age (years; median and range)	59 (28–82)	59 (20–82)
Sex		
Male	497 (72%)	473 (68%)
Female	197 (28%)	224 (32%)
Ethnic origin		
Caucasian	410 (59%)	417 (60%)
East Asian	259 (37%)	252 (36%)
Other	25 (4%)	28 (4%)
Smoking history*		
Smoker	536 (77%)	524 (75%)
Current smoker	259 (37%)	242 (35%)
Former smoker	276 (40%)	282 (40%)
Non-smoker	158 (23%)	173 (25%)
WHO performance status		
0	250 (36%)	238 (34%)
1	436 (63%)	451 (65%)
Other†	8 (1%)	8 (1%)
Histology		
Adenocarcinoma	412 (59%)	417 (60%)
Squamous	184 (27%)	160 (23%)
Other‡	98 (14%)	120 (17%)
Stage of disease§		
Stage IIIb	95 (14%)	106 (15%)
Stage IV	598 (86%)	590 (85%)
Brain metastases	65 (9%)	80 (11%)
Previous chemotherapy		
Platinum compound	660 (95%)	664 (95%)
Pyrimidine analogue	308 (44%)	314 (45%)
Taxane	216 (31%)	209 (30%)
Vinca alkaloid or analogue	124 (18%)	122 (18%)
Best response to first-line chemotherapy		
Complete response	14 (2%)	13 (2%)
Partial response	217 (31%)	216 (31%)
Stable disease	252 (36%)	260 (37%)
Progressive disease	168 (24%)	170 (24%)

	Vandetanib+docetaxel (n=694)	Placebo+docetaxel (n=697)
Non-evaluable	16 (2%)	15 (2%)
Not applicable or not recorded	27 (4%)	23 (3%)
Prior bevacizumab	20 (3%)	24 (3%)

ITT=intention-to-treat. Data are n (%), unless stated otherwise.

* Smoker: includes ex-smoker (stopped smoking ≥ 365 days), occasional smoker (<1 tobacco product per day), and habitual smoker (≥ 1 tobacco product per day). Nonsmoker: patients who have smoked ≤ 20 g of tobacco in lifetime.

[†] WHO performance status 2 at entry: six (vandetanib) and two (placebo). Not recorded: two (vandetanib) and six (placebo).

[‡] Includes adenosquamous carcinoma, large-cell carcinoma, and non-small-cell lung cancer not further classified.

[§] Not recorded for one patient in each group.

Table 2

Adverse events reported in at least 10% of patients in either group (safety population)

	Vandetanib+docetaxel (n=689)		Placebo+docetaxel (n=690)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	289 (42%)	35 (5%)	225 (33%)	28 (4%)
Alopecia	230 (33%)	0	240 (35%)	0
Rash	291 (42%)	63 (9%)	167 (24%)	7 (1%)
Fatigue	209 (30%)	36 (5%)	215 (31%)	36 (5%)
Neutropenia	221 (32%)	199 (29%)	184 (27%)	164 (24%)
Anorexia	200 (29%)	14 (2%)	205 (30%)	10 (1%)
Nausea	159 (23%)	0	220 (32%)	0
Cough	130 (19%)	0	131 (19%)	0
Dyspnoea	119 (17%)	40 (6%)	142 (21%)	51 (7%)
Constipation	118 (17%)	0	140 (20%)	0
Pyrexia	135 (20%)	0	119 (17%)	0
Vomiting	107 (16%)	0	143 (21%)	0
Leukopenia	127 (18%)	99 (14%)	108 (16%)	77 (11%)
Asthenia	107 (16%)	21 (3%)	93 (13%)	18 (3%)
Anaemia	71 (10%)	14 (2%)	103 (15%)	29 (4%)
Myalgia	90 (13%)	0	78 (11%)	0
Insomnia	93 (13%)	0	73 (11%)	0
Stomatitis	82 (12%)	0	80 (12%)	0

Data are n (%). Adverse events are the Medical Dictionary for Regulatory Activities preferred term.