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Drug substance(s):	ZD6474		
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A Randomized, Partially Blinded, Phase II Study to Assess the Safety, Tolerability, and Efficacy of ZD6474 Alone or in Combination with Paclitaxel and Carboplatin in Patients with Previously Untreated Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC)

International co-ordinating investigator

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Study center(s)

This study was conducted in 2 phases, a safety run-in phase and a randomized phase. The run-in phase was conducted at 8 centers in the US. The randomized phase was initiated at 35 centers in 9 countries (Finland [2 centers], France [5 centers], Germany [2 centers], India [1 center], Italy [2 centers], South Africa [5 centers], Spain [4 centers], Thailand [1 center], and the US [13 centers]).

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	Run-in: 12 Feb 2004 Randomized: 04 Nov 2004	Therapeutic exploratory (II)
Last patient completed	31 Oct 2007	

Objectives

Run-in phase:

The primary objective of the safety run-in phase was to establish the appropriate and tolerable dose of ZD6474 (ZACTIMA™, vandetanib), hereafter referred to as ZACTIMA, to be administered in combination with the chemotherapy regimen of paclitaxel and carboplatin in patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC).

The secondary objective of the safety run-in phase was to explore the pharmacokinetics of ZACTIMA, paclitaxel, and carboplatin administered alone and in combination in patients with previously untreated locally advanced or metastatic NSCLC, and compare these parameters with the existing AstraZeneca database. Additionally, the survival of patients was assessed.

Randomized phase:

The primary objective of the randomized phase was to determine the efficacy of ZACTIMA alone (300 mg daily orally [PO]), paclitaxel/carboplatin, and ZACTIMA in combination with paclitaxel/carboplatin, in prolonging the progression-free survival (PFS) of patients with previously untreated locally advanced or metastatic NSCLC.

The secondary objectives of the randomized phase were:

1. To define the objective tumor response rates (complete response [CR] and partial response, [PR]) and disease control rates (CR + PR + stable disease; stable disease [SD]≥12 weeks) in patients with previously untreated locally advanced or metastatic NSCLC treated with ZACTIMA alone (300 mg daily PO), paclitaxel/carboplatin, and ZACTIMA in combination with paclitaxel/carboplatin;

2. To study the tolerability and safety of ZACTIMA alone (300 mg daily PO) or ZACTIMA combined with paclitaxel/carboplatin, compared with paclitaxel/carboplatin;

3. To investigate the pharmacokinetics of ZACTIMA, paclitaxel, and carboplatin to evaluate changes in plasma exposure when ZACTIMA is administered in combination compared to when given alone and to further investigate the relationship between plasma exposure and safety and biological activity, in order to see whether any change in plasma exposure is clinically meaningful;

4. To determine the overall survival of patients treated with ZACTIMA alone (300 mg PO daily), ZACTIMA in combination with paclitaxel and carboplatin, or paclitaxel and carboplatin by assessment of time to death;

5. To investigate the effect of ZACTIMA alone (300 mg daily PO) or ZACTIMA in combination with paclitaxel/carboplatin, compared with paclitaxel/carboplatin on quality of life (Functional Assessment of Cancer Therapy for Lung Cancer

[FACT-L]), symptom improvement (lung cancer subscale, LCS), and World Health Organization (WHO) performance status.

The exploratory objectives of the randomized phase were:

1. To explore potential pharmacodynamic biomarkers from blood including levels of angiogenic factors (vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF]) and circulating endothelial cells (CECs), and determine if pre-treatment levels or treatment-induced changes in these markers correlated with clinical outcome. Additional blood protein markers of ZACTIMA pharmacological activity, or anti-tumor effects could be identified and measured if scientific or technological advances meant that less blood sample volume was required to measure VEGF and bFGF, and/or if scientific advances identified such additional blood protein markers;

2. To explore changes in pharmacodynamic biomarkers (VEGF and EGF receptors [VEGFR, EGFR]) in the tumor compared to baseline and determine if pre-treatment expression or treatment-induced changes in these markers correlated with clinical outcome. Additional histological markers of ZACTIMA pharmacological activity, or anti-tumor effects, could be measured if technological advances allowed a smaller proportion of the tumor samples to be used to determine the effects of ZACTIMA on the EGF and VEGF receptors, and/or if scientific advances identified such additional histological markers.

3. To explore the potential relationship between the EGFR gene mutation and clinical outcomes.

Study design

This was a phase II, randomized, partially blinded multicenter study assessing the safety, tolerability and efficacy of ZACTIMA alone or in combination with paclitaxel and carboplatin in patients with previously untreated locally advanced or metastatic NSCLC. The study was conducted in 2 phases: a safety run-in phase and a randomized phase.

Phase I/II data have shown that chronic administration of both 200 mg and 300 mg of ZACTIMA as monotherapy is well tolerated. The safety run-in phase was designed to detect any acute toxicity or interaction between ZACTIMA and paclitaxel/carboplatin. Based on the results of the safety run-in phase, an internal AstraZeneca Data Safety Monitoring Board (DSMB) recommended 300-mg ZACTIMA as an appropriate and tolerable dose to be used in combination with paclitaxel/carboplatin in the randomized phase of the study.

Interim analysis

A planned interim review of data from the first 60 patients enrolled in the randomized phase was conducted after 12 weeks of follow-up to compare the monotherapy arm to paclitaxel/carboplatin alone based on PFS. Recruitment was continued during follow-up for the interim analysis. The analysis of the data showed that the PFS hazard ratio of the

ZACTIMA monotherapy treatment arm was >1.33. This was the protocol-designated hazard ratio beyond which recruitment to the monotherapy arm was to be discontinued. Based on this result, the investigators were notified of the results of the analysis and recruitment to the monotherapy treatment arm was stopped.

Target patient population

Patients with histologically or cytologically confirmed locally advanced (IIIb with pleural effusion) or metastatic (IV) NSCLC suitable for first-line therapy with paclitaxel/carboplatin and ZACTIMA with no prior chemotherapy, biological therapy, or radiation therapy (not including adjuvant or neoadjuvant therapy, radiation to the brain, or radiation to a bone metastasis for palliation). Patients with early stage NSCLC (I-III) that relapsed in the non-resectable metastatic site who had not received chemotherapy or chest radiotherapy were also eligible.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Tablet strength (mg)	Formulation number	Description
50-mg ZACTIMA	F013028	White film-coated, round 6 mm
100-mg ZACTIMA	F013025	White film-coated, round 10 mm
Placebo to match 100-mg ZACTIMA	F013044	White film-coated, round 10 mm

ZACTIMA or matching placebo (2 x 100 mg or 3 x 100 mg in tablet form) was dosed orally, once daily, preferably at the same time of day each morning. Paclitaxel (200 mg/m^2) administered intravenously (IV) over 3 hours in Cycle 1 and over 60 to 90 minutes in all subsequent cycles; carboplatin (AUC_{SS} 6) was administered IV over 30 to 60 minutes in all cycles. Paclitaxel and carboplatin were administered every 3 weeks for a maximum of 6 cycles.

Duration of treatment

Each treatment cycle was 21 days in duration for both the run-in and randomized phases of the study. In the safety run-in phase, patients with a CR, PR, or SD after 6 cycles of therapy continued on ZACTIMA as a single agent until meeting the criteria of discontinuation. In the randomized phase, recruitment to the monotherapy treatment arm was stopped after the interim analysis, but patients who were receiving clinical benefit could continue on ZACTIMA monotherapy with Institutional Review Board (IRB) approval. Patients received a maximum of 6 cycles of chemotherapy (as part of their combination therapy). Patients who achieved a CR, PR, or SD after 6 cycles of combination therapy continued on either ZACTIMA or placebo as a single agent until meeting the criteria of discontinuation.

Criteria for evaluation (main variables)

Run-in phase:

- Primary/safety: Incidence, Common Terminology Criteria for Adverse Events (CTCAE) grade, and type of adverse events (AEs); clinically significant laboratory abnormalities or changes in vital signs; and electrocardiographic (ECG) changes.

- Secondary/pharmacokinetic (PK): ZACTIMA maximum steady state concentration during the dosing interval (C_{ssmax}), total clearance (CL), area under the concentration time curve during the dosing interval at steady state (AUC_{ss}), and volume of distribution at steady state (V_{ss}); paclitaxel plasma concentration at end of infusion (C_{inf}), CL, V_{ss}, and terminal half life ($t_{1/2}$); carboplatin C_{inf}, CL, V_{ss}, and $t_{1/2}$ of free and total carboplatin.

Randomized phase:

Efficacy and pharmacokinetics

- Primary variable/efficacy: progression-free survival (PFS)

- Secondary variables/efficacy: Objective response rate (CR + PR) and disease control rate (CR + PR + SD≥12 weeks) based on Response Evaluation Criteria in Solid Tumors (RECIST); quality of life (QoL) and LCS from the FACT-L questionnaire; WHO performance status; and time to death.

- Secondary variables/PK: ZACTIMA C_{ssmax}, AUC_{ss}, CL, and $V_{ss;}$ paclitaxel C_{inf}, CL, V_{ss}, and $t_{1/2}$; carboplatin C_{inf}, CL, V_{ss}, and $t_{1/2}$ of total platinum

- Secondary variables/pharmacodynamics (PD): Probability of risk of QTc prolongation and of the concentration of ZACTIMA; and exploration of the relationship between ZACTIMA and chemotherapy exposure and measures of safety and biological activity

- Exploratory variables: Blood PD biomarkers: VEGF, bFGF, and CECs; tumor sample PD biomarkers: VEGFR/angiogenesis, kinase insert domain receptor (KDR), phospho-KDR, platelet endothelial cell adhesion molecule (CD31 [or vWF]); proliferation: Ki67; apoptosis: M30 and TUNEL; EGFR signal transduction: EGFR, phospho-EGFR, mitogen-activated protein kinase (MAPK), phospho-MAPK, AKT, phospho-AKT; and EGFR gene mutation and clinical outcomes

Safety

Safety was not a primary endpoint for the randomized phase of this study. The secondary safety variables were incidence, CTCAE grade, and type of AEs; clinically significant laboratory abnormalities or changes in vital signs; and ECG changes.

Statistical methods

Run-in phase:

In the safety run-in phase, the objective was to establish the appropriate and tolerable dose of ZACTIMA between 2 doses (200 mg and 300 mg) to be used in combination with paclitaxel and carboplatin. Descriptive statistics were employed to make the assessment in the safety run-in phase. Twenty-five patients were enrolled to obtain a minimum of 10 patients evaluated at each of the doses actually considered. The dose-escalation decision in the safety run-in phase was based on the incidence, severity, and causality of AEs observed during the first 6 weeks of treatment.

Randomized phase:

The primary objective of the randomized phase was to assess the efficacy of ZACTIMA 300 mg PO daily (dose determined from the run-in) as monotherapy, 300-mg ZACTIMA + paclitaxel + carboplatin, and paclitaxel + carboplatin only. The randomized phase of the study assessed the efficacy of the 3 arms of the study by comparing PFS.

In this study, a 1-sided p-value of less than 0.2 was considered evidence that the new agent showed sufficient promise to warrant further investigation. The sample size for the randomized portion of the study was based on the primary endpoint, PFS; approximately 200 patients were planned for enrollment. A total of 181 patients were recruited (2:1:1 randomization in 300-mg ZACTIMA alone, 300-mg ZACTIMA + paclitaxel/carboplatin, and placebo + paclitaxel/carboplatin arms, respectively) into the randomized phase of the study. Using a non-inferiority margin derived from a meta-analysis of Cisplatin versus best supportive care (HR=0.73), this trial was sized to have 75% power to demonstrate non-inferiority (1-sided 20% significance level) for the comparison of 300-mg ZACTIMA versus placebo + paclitaxel/carboplatin. Also, this trial was sized to have 75% power to detect a 30% reduction in the risk of progression for 300-mg ZACTIMA + paclitaxel/carboplatin in relation to placebo + paclitaxel/carboplatin (ie, HR of 70%) with a 1-sided 20% significance level. A 1-sided p-value of <0.2 was considered to demonstrate activity of ZACTIMA that would warrant further study.

When 60 patients had completed 12 weeks of treatment in the randomized phase, a preplanned interim analysis of PFS compared 300-mg ZACTIMA monotherapy versus placebo + paclitaxel/carboplatin. Because the observed PFS hazard ratio was >1.33, recruitment to the 300-mg ZACTIMA monotherapy arm was stopped and treatment discontinued unless the patient was receiving clinical benefit. The results presented in this report focus on that of the combination treatment arms (300-mg ZACTIMA + paclitaxel/carboplatin versus placebo + paclitaxel/carboplatin).

At the time of the analysis of the primary endpoint of PFS (data cutoff of 30 April 2006), overall survival was also analyzed. In addition, a mature survival analysis was performed when approximately 75% of patients had died (data cutoff of 30 June 2007). Though not prespecified in the statistical analysis plan (SAP), results of the analysis of PFS as well as

objective response and disease control rates using the final data cutoff date of 30 June 2007 were also presented.

Patient population

Twenty-five patients were sequentially recruited into the run-in phase of this study. Of these, 15 patients received 200-mg ZACTIMA + paclitaxel/carboplatin and 10 patients received 300-mg ZACTIMA + paclitaxel/carboplatin. The treatment arms were generally similar in terms of demographics and baseline characteristics. There were more males than females and the majority of patients were Caucasian.

Of the 181 patients enrolled into the randomized phase of this study, 73 patients were randomized to 300-mg ZD6474 monotherapy. Demographic and baseline characteristics for the monotherapy treatment arm were generally similar to that observed for the ZD6474 + paclitaxel/carboplatin and placebo + paclitaxel/carboplatin treatment arms.

Fifty-six patients were randomized to 300-mg ZACTIMA + paclitaxel/carboplatin and 52 patients were randomized to placebo + paclitaxel/carboplatin. The treatment groups were generally well balanced in terms of demographics and baseline characteristics. Overall, there were more males (70.4%) than females (29.6%) and the majority of patients were Caucasian (93.5%). The mean age for this study population was 59.9 years with the majority of patients younger than 65 years of age (71.3%). Patient disposition was similar between the 300-mg ZACTIMA + paclitaxel/carboplatin and placebo + paclitaxel/carboplatin treatment arms. At the time of initial data cutoff (30 April 2006), 52% of patients had died; at the time of final data cutoff (30 June 2007), 82% and 73% of patients in the 300-mg ZACTIMA + paclitaxel/carboplatin and paclitaxel/carboplatin alone had died.

Table S1 Patient population and disposition - randomized phase (combination treatment arms)

		300-mg ZACTIMA + paclitaxel / carboplatin		**Placebo + paclitaxel / carboplatin**		**Total**	
Population							
N randomized		56		52		108	
Demographic characteristics							
Sex (n and % of patients)	Male	39	(69.6)	37	(71.2)	76	(70.4)
	Female	17	(30.4)	15	(28.8)	32	(29.6)
Age (years)	Mean (SD)	59.8	(8.52)	59.9	(9.01)	59.9	(8.72)
	Range	36 to 79		42 to 83		36 to 83	

Table S1 Patient population and disposition - randomized phase (combination treatment arms)

		300-mg ZACTIMA + paclitaxel / carboplatin		Placebo + paclitaxel / carboplatin		Total	
Age category (n and % of patients)	≥18 to <65	39	(69.6)	38	(73.1)	77	(71.3)
	≥65 to <75	14	(25.0)	9	(17.3)	23	(21.3)
	≥75	3	(5.4)	5	(9.6)	8	(7.4)
Race (n and % of patients)	Caucasian	51	(91.1)	50	(96.2)	101	(93.5)
	Black	2	(3.6)	1	(1.9)	3	(2.8)
	Asian	2	(3.6)	0		2	(1.9)
	Other	1	(1.8)	1	(1.9)	2	(1.9)
Baseline characteristics (n and % of patients)							
Disease metastasis							
Distant metastatic		49	(87.5)	46	(88.5)	95	(88.0)
Locally advanced only		7	(12.5)	6	(11.5)	13	(12.0)
WHO performance status							
0 (Normal activity)		25	(44.6)	16	(30.8)	41	(38.0)
1 (Restricted activity)		31	(55.4)	36	(69.2)	67	(62.0)
Tumor histology							
Squamous cell carcinoma grouping		11	(19.6)	15	(28.8)	26	(24.1)
Non-squamous cell carcinoma grouping		45	(80.4)	37	(71.2)	82	(75.9)
Squamous cell carcinoma		10	(17.9)	15	(28.8)	25	(23.1)
Adenocarcinoma		33	(58.9)	26	(50.0)	59	(54.6)
Adenocarcinoma bronchoalveolar		2	(3.6)	1	(1.9)	3	(2.8)
Large cell carcinoma		4	(7.1)	5	(9.6)	9	(8.3)
Adenosquamous carcinoma		1	(1.8)	0		1	(0.9)
Other		6	(10.7)	5	(9.6)	11	(10.2)

Table S1 Patient population and disposition - randomized phase (combination treatment arms)

	300-mg ZACTIMA + paclitaxel / carboplatin		Placebo + paclitaxel / carboplatin		Total	
Disease stage						
IIIb	7	(12.5)	5	(9.6)	12	(11.1)
IV	49	(87.5)	47	(90.4)	96	(88.9)
Smoking status						
Non-smoker	13	(23.2)	11	(21.2)	24	(22.2)
Ex-smoker	31	(55.4)	25	(48.1)	56	(51.9)
Occasional smoker	0		4	(7.7)	4	(3.7)
Habitual smoker	12	(21.4)	11	(21.2)	23	(21.3)
Not done	0		1	(1.9)	1	(0.9)
N analyzed for safety[a]	56		52		108	
N analyzed for efficacy (ITT)	56		52		108	

ITT Intention-to-treat; n Number of patients in each category; N Number.

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.

Note: Non-smoker includes former smoker (no cigarettes for past 5 years); occasional smoker (<1 cigarette per day or smokers who have ceased smoking from 6 months through 4 years); and habitual smoker (>1 cigarette per day or cessation of smoking for <6 months)

Efficacy and pharmacokinetic results - randomized phase (combination treatment arms)

Based on the results of the run-in phase of the study, a dose of 300 mg was chosen as the appropriate and tolerable dose of ZACTIMA to be used in the randomized phase of the study. A planned interim review of data from the first 60 patients enrolled in the randomized phase phase after 12 weeks of follow-up was conducted to compare the monotherapy arm to paclitaxel/carboplatin alone based on PFS. Recruitment was continued during follow-up for the interim analysis. The analysis of the data showed that the PFS hazard ratio of the ZACTIMA monotherapy treatment arm was >1.33. This was the protocol-designated hazard ratio beyond which recruitment to the monotherapy arm was to be discontinued Based on this result, the investigators were notified of the results of the analysis and recruitment to the monotherapy treatment arm was stopped. Patients could remain on 300-mg ZACTIMA if the patient was receiving clinical benefit. Eight patients discontinued treatment with 300-mg ZACTIMA monotherapy when the results of the analysis were known.

The primary objective of this study was to assess the efficacy of ZACTIMA (300 mg PO daily) in combination with paclitaxel/carboplatin compared with the efficacy of paclitaxel/carboplatin alone in prolonging PFS in patients with locally advanced or metastatic

NSCLC. The primary analysis of PFS was done using the Cox proportional hazards regression model. The nominal significance level of this study was 20%, which was used as the statistical threshold to determine whether results would warrant further investigation.

Treatment with 300-mg ZACTIMA combined with paclitaxel/carboplatin significantly reduced the risk of disease progression over a given period of time by approximately 24% compared to paclitaxel/carboplatin alone (HR=0.76; 2-sided 95%CI=0.50, 1.15). The 1-sided p-value of 0.098 was statistically significant at the nominal level of 0.2 set for this study.

At the time of final data cutoff (30 June 2007), no statistically significant difference in overall survival was seen between 300-mg ZACTIMA in combination with paclitaxel/carboplatin compared to paclitaxel/carboplatin alone (HR=1.150; 2-sided 95% CI=0.748, 1.770).

There was a greater objective response rate observed in the 300-mg ZACTIMA + paclitaxel/carboplatin treatment arm than in paclitaxel/carboplatin alone (32.1% vs. 25.0%). Patients in the 300-mg ZACTIMA + paclitaxel/carboplatin treatment arm were approximately 1.5 times more likely to experience an objective tumor response compared to those in the paclitaxel/carboplatin alone arm (odds ratio of 1.549, 2-sided 95% CI: 0.655, 3.664); this increase was statistically significant at the significance level of 0.2 set for this study (p=0.160). However, the rate of disease control ≥12 weeks was similar between the treatments (57.1% and 57.7%, respectively). There was no statistical difference between treatments in the odds of disease control ≥12 weeks.

No statistically significant difference was observed between treatments in QoL as assessed by LCS scores (estimated difference of -0.405 for 300-mg ZACTIMA + paclitaxel/carboplatin over paclitaxel/carboplatin alone; 2-sided 95% CI: -1.02, 0.211, 1-sided p=0.710). Similarly, no statistically significant difference was observed for TOI scores (estimated difference of -2.638; 2-sided 95% CI: -4.48 to 0.795, 1-sided p=0.885).

Pharmacokinetic results showed that ZACTIMA administered once daily had a mean apparent clearance of 11.3 ± 0.5 $L.h^{-1}$ and a mean half-life of approximately 8 days. The estimated PK suggested an 11-fold accumulation of drug from single dose to steady state (range of 2- to 40-fold). The estimated time to PK steady state was approximately 1 month and an average plasma concentration of 1165 ng/mL was estimated for continuous monthly administration of ZACTIMA 300 mg. There was no influence of combination therapy (paclitaxel/carboplatin) on the estimated clearance of ZACTIMA.

A non-linear PK/QTc relationship was observed, such that a maximum change of 25 to 30 ms was reached within 1 month of dosing; high residual variability (± 17 ms at baseline) was observed. No relationship to AEs could be established due to the limited number of subjects experiencing rash and/or diarrhea, and no correlation between efficacy and PK was evident.

No PK analysis of carboplatin or paclitaxel could be undertaken due to limited sampling.

Safety results - randomized phase (combination treatment arms)

Overall, the safety profile of ZACTIMA was similar to that observed in other ZACTIMA studies.

Table S2 Number of patients who had at least 1 adverse event in any category - randomized phase (safety analysis set)

Category of adverse event	Number (%) of patients					
	300-mg ZACTIMA + paclitaxel / carboplatin (N=56)		Placebo + paclitaxel / carboplatin (N=52)		Total (N=108)	
Any AEs	55	(98.2)	52	(100.0)	107	(99.1)
Any AE of CTCAE grade 3 or higher	45	(80.4)	37	(71.2)	82	(75.9)
SAEs	29	(51.8)	14	(26.9)	43	(39.8)
Any SAEs leading to death	4	(7.1)	0		4	(3.7)
Any SAEs not leading to death	27	(48.2)	14	(26.9)	41	(38.0)
Discontinuations of study treatment due to AEs	24	(42.9)	13	(25.0)	37	(34.3)
Other significant AEs	14	(25.0)	14	(26.9)	28	(25.9)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

As of final data cutoff on 30 June 2007.

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; N Number of patients in each treatment group; SAE Serious adverse event.

Table S3 Incidence of most commonly reported adverse events (≥10% in either treatment group) (safety analysis set)

MedDRA preferred term	Number (%) of patients			
	300-mg ZACTIMA + paclitaxel / carboplatin (N=56)		Placebo + paclitaxel / carboplatin (N=52)	
Diarrhea	29	(51.8)	17	(32.7)
Rash	28	(50.0)	13	(25.0)
Neutropenia	24	(42.9)	23	(44.2)
Fatigue	23	(41.1)	21	(40.4)
Constipation	22	(39.3)	19	(36.5)
Alopecia	19	(33.9)	25	(48.1)

Table S3 Incidence of most commonly reported adverse events (≥10% in either treatment group) (safety analysis set)

MedDRA preferred term	Number (%) of patients			
	300-mg ZACTIMA + paclitaxel / carboplatin (N=56)		Placebo + paclitaxel / carboplatin (N=52)	
Hypertension	18	(32.1)	2	(3.8)
Nausea	18	(32.1)	26	(50.0)
Insomnia	17	(30.4)	7	(13.5)
Thrombocytopenia	16	(28.6)	13	(25.0)
Anorexia	14	(25.0)	7	(13.5)
Cough	13	(23.2)	10	(19.2)
Dyspnea	13	(23.2)	11	(21.2)
Peripheral sensory neuropathy	12	(21.4)	11	(21.2)
Vomiting	12	(21.4)	16	(30.8)
Weight decreased	12	(21.4)	3	(5.8)
Asthenia	11	(19.6)	7	(13.5)
Depression	10	(17.9)	3	(5.8)
Electrocardiogram QTc interval prolonged	10	(17.9)	0	
Anemia	9	(16.1)	17	(32.7)
Mucosal inflammation	9	(16.1)	6	(11.5)
Pain in extremity	9	(16.1)	4	(7.7)
Myalgia	8	(14.3)	15	(28.8)
Pyrexia	8	(14.3)	15	(28.8)
Back pain	7	(12.5)	5	(9.6)
Leukopenia	7	(12.5)	4	(7.7)
Polyneuropathy	7	(12.5)	4	(7.7)
Arthralgia	6	(10.7)	14	(26.9)
Dry skin	6	(10.7)	2	(3.8)
Dysphonia	6	(10.7)	3	(5.8)
Hemoptysis	6	(10.7)	2	(3.8)
Headache	6	(10.7)	5	(9.6)
Hypokalemia	6	(10.7)	4	(7.7)
Hypomagnesemia	6	(10.7)	4	(7.7)

Table S3 Incidence of most commonly reported adverse events (≥10% in either treatment group) (safety analysis set)

MedDRA preferred term	Number (%) of patients			
	300-mg ZACTIMA + paclitaxel / carboplatin (N=56)		Placebo + paclitaxel / carboplatin (N=52)	
Neuropathy	6	(10.7)	3	(5.8)
Edema peripheral	6	(10.7)	6	(11.5)
Pain	6	(10.7)	4	(7.7)
Arthralgia	5	(8.9)	14	(26.9)
Epitaxis	4	(7.1)	6	(11.5)
Paresthesia	4	(7.1)	6	(11.5)
Musculoskeletal chest pain	3	(5.4)	6	(11.5)
Musculoskeletal pain	3	(5.4)	7	(13.5)
Dyspepsia	2	(3.6)	6	(11.5)

As of final data cutoff on 30 June 2007.
Note: Presented in descending frequency of incidence within the 300-mg ZACTIMA + paclitaxel/carboplatin treatment group.
N Number of patients in each treatment group.

More patients in the 300-mg ZACTIMA + paclitaxel/carboplatin treatment arm had serious adverse events (SAEs) (51.8% vs. 26.9%), discontinued treatment as a result of AEs (42.9% vs. 25.0%) , and had AEs of CTCAE grade 3 or higher (80.4% vs. 71.2%) compared to the placebo + paclitaxel/carboplatin treatment arm. The most common AEs were diarrhea, rash, neutropenia, and fatigue. Expected AEs occurring more frequently in the ZACTIMA group were diarrhea (51.8% vs. 32.7%), rash (50.0% vs. 25.0%), hypertension (32.1% vs. 3.8%), and prolonged QTc interval (17.9% vs. 0%). Neutropenia was the most frequently reported AE with CTC grade ≥3 (35.7% vs. 34.6%).

A 2- to 3-fold increase was observed in the incidence of insomnia (30.4% vs. 13.5%), anorexia (25.0% vs. 13.5%), weight loss (21.4% vs. 5.8%), and depression (17.9% vs. 5.8%). There were no increased incidences in arrhythmias or thromboembolism between the 2 treatment arms. No intracranial bleeding or interstitial lung disease (ILD) was observed with either treatment group.

Most deaths were due to disease progression. Other causes of death (SAEs leading to death) observed in this study could be expected in a lung cancer population with its associated comorbidities (respiratory failure, multi-organ failure, pulmonary embolism, and sepsis). Overall, 4 patients in the 300-mg ZACTIMA + paclitaxel/carboplatin treatment arm had SAEs

leading to death (listed immediately above) as compared to none treated with paclitaxel/carboplatin alone.

Clinical laboratory abnormalities observed on the study were manageable. Changes in leukocyte, neutrophil, hemoglobin, and platelet values were expected as a result of chemotherapy. The expected increased incidence of neutropenia occurred at a similar rate between the arms based on the number of patients who had a CTCAE grade shift from ≤2 to ≥3. Despite the increased incidence of neutropenia, the relevant outcome (neutropenic fever) was relatively rare. The incidences of proteinuria and hematuria were low and were similar between the 2 treatment groups (<4%).

Potentially clinically significant weight loss (≥10% decrease from baseline) and elevations in systolic and diastolic blood pressure were observed more frequently in the 300-mg ZACTIMA + paclitaxel/carboplatin arm compared with paclitaxel/carboplatin alone. A 2-fold increase in the AE incidence of anorexia was observed for patients treated with ZACTIMA (25.0% vs. 13.5%) and a nearly 10-fold increase was observed in reported AEs of hypertension (32.1% vs. 3.8%) compared with those treated with paclitaxel/carboplatin alone; however, the hypertension in the ZACTIMA arm was CTC grade 1 or 2 in the majority (14 of 18) of patients. The incidence of QTc prolongation was higher in the ZACTIMA treatment arm; however, all QTc prolongations were clinically asymptomatic and the protocol-defined prolongations were manageable with the protocol-defined regimen for handling QTc prolongation. The effect of taking prohibited concomitant medications known to prolong the QT interval (5-hyroxytriptamine-3 [5HT-3] antagonists) was not clear.

Conclusions

- The study met the primary objective of prolongation of PFS ($p<0.2$) for ZACTIMA + paclitaxel/carboplatin compared to paclitaxel/carboplatin alone.
- There was no statistically significant difference in overall survival between the treatment arm with 300-mg ZACTIMA in combination with paclitaxel/carboplatin and the arm with paclitaxel/carboplatin alone.
- In this study, 300-mg ZACTIMA (in combination with paclitaxel/carboplatin) was well tolerated by the majority of patients. The AEs observed were generally consistent with those observed in other ZACTIMA studies.

Date of the report

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