Drug product:	IRESSA™ 250 mg	**SYNOPSIS**	
Drug substance(s):	Gefitinib (ZD1839)		
Study code:	D791AC00001		
Date:	18 April 2007		

A randomised, open label, parallel group, multi-centre, phase II study of progression-free survival comparing ZD1839 (IRESSA™) (250 mg tablet) versus vinorelbine (30 mg/m^2 infusion) in chemonaïve, elderly patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC

INVITE (Iressa in NSCLC versus Vinorelbine Investigation in The Elderly)

Study centres

This study was conducted at 41 centres in 10 countries: Australia (4 centres), Brazil (1 centre); Czech Republic (6 centres), France (1 centre), Germany (8 centres), Italy (8 centres), Korea (3 centres), South Africa (1 centre), Taiwan (2 centres), and United Kingdom (7 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	08 July 2004	Therapeutic exploratory (II)
Last patient enrolled	08 December 2005	
Date of data cut-off	24 February 2006	

Objectives

The primary objective of this study was to compare gefitinib and vinorelbine in terms of progression-free survival (PFS).

Secondary objectives were:

- To compare gefitinib and vinorelbine in terms of pulmonary symptom improvement (PSI)
- To compare gefitinib and vinorelbine in terms of quality of life (QoL)
- To describe gefitinib and vinorelbine in terms of adverse event (AE) profile
- To compare gefitinib and vinorelbine in terms of overall objective tumour response rate (complete response [CR] and partial response [PR])
- To compare gefitinib and vinorelbine in terms of overall survival (OS)

Exploratory objectives of the study were:

- To investigate the correlation of the expression of biomarkers in tumour tissue obtained prior to gefitinib therapy with gefitinib clinical efficacy, and to determine a set of biomarkers to enable patient selection for therapy
- To obtain blood samples for DNA extraction for possible future pharmacogenetic analysis and other potential correlative markers of the activity of gefitinib
- To compare gefitinib and vinorelbine in terms of changes in pain and fatigue
- To investigate patient satisfaction with their treatment (UK only)

Study design

This was a randomised, open label, parallel group, multi-centre phase II study of PFS, comparing gefitinib (250 mg orally once daily) to vinorelbine (30 mg/m^2 intravenously on Days 1 and 8 of a 21-day cycle) in chemonaïve, elderly patients with locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC). Patients were randomised to treatment in a 1:1 ratio.

Target patient population and sample size

The target population was male or female patients aged ≥70 years with histologically-confirmed locally advanced (stage IIIB) or metastatic (stage IV) NSCLC who had not received prior chemotherapy, biological or immunological therapy. Patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), and a World Health Organisation (WHO) performance status ≤2, and to be prepared to provide a histological biopsy sample from the original tumour or metastatic site for biomarker analysis.

Sample size calculations were based on PFS (the primary endpoint). The median PFS for patients treated with vinorelbine was expected to be approximately 3 months, and the study

was designed to detect a hazard ratio (vinorelbine:gefitinib) of 1.5, which would imply a median PFS of 4.5 months for patients treated with gefitinib. A total of 151 progression events was estimated to be sufficient to detect this difference with 80% power, assuming the 2-sided alpha level was 10%. One-hundred and ninety-two randomised patients (96 per treatment group) recruited over an 18-month period and followed up for 6 months was estimated to be sufficient to observe 151 progression events.

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

The investigational product was gefitinib (ZD1839; IRESSA™): 250 mg (one tablet) was taken orally once daily. Gefitinib was supplied by AstraZeneca. The formulation (batch) numbers for the tablets used in this study were F12653 (10909G03, 11837J03, 12328G03, 13005J03, 21063J04, 21510C04) and PP001327 (90539A02 and 10257F03).

The comparator was commercially-available vinorelbine (manufactured by Fabre, Baxter/Asta Medica, and Orient Europharma): 30 mg/m^2 was administered intravenously as a slow bolus injection or short infusion on Days 1 and 8 of a 21-day cycle. Vinorelbine was supplied by either AstraZeneca or the investigators' pharmacies. The formulation (batch) numbers are listed in Appendix 12.1.6.

Duration of treatment

Patients received gefitinib until clinical or objective progression, unacceptable toxicity, or patient refusal (whichever occurred first). At the point of disease progression, further therapy was at the discretion of the investigator and patient; patients could continue to receive gefitinib if they were deriving clinical benefit (these patients were followed up for safety information).

Patients received vinorelbine for up to a maximum of 6 cycles, or until clinical or objective progression, unacceptable toxicity, or patient refusal (whichever occurred first). At the point of disease progression, further therapy was at the discretion of the investigator and patient.

The study continued until 151 progression events had occurred. At this point, patients could continue to receive gefitinib if they were deriving clinical benefit (these patients were subsequently switched to a named-patient supply and followed up for serious AEs [SAEs]). Safety data for patients who continued to receive study treatment after study closure are reported in Appendix 12.1.14.

Criteria for evaluation (main variables)

Efficacy and patient-reported outcomes (PROs)

- Primary variable: PFS (defined as the interval between the date of randomisation and the earliest date of objective disease progression [as assessed by RECIST] or death due to any cause in the absence of progression)

- Secondary efficacy variables:
  - Overall best confirmed objective tumour response (CR and PR) as assessed by RECIST
  - OS (time to death; defined as the interval between the date of randomisation and the date of patient death due to any cause)
- Secondary PRO variables:
  - PSI as measured by the 4 pulmonary items of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) Lung Cancer Subscale (LCS); the 4 pulmonary items are shortness of breath, ease of breathing, tightness in chest, and cough
  - Patient-reported functionality as measured by the Trial Outcome Index (TOI; the TOI comprises the Physical and Functional Well-being sections and LCS domain of the FACT-L) and QoL as measured by the FACT-L total score; also disease-related symptoms as measured by the LCS domain of the FACT-L (described in the Statistical Analysis Plan [SAP])

Safety

- Secondary variable: the AE profile based on the type, frequency, and severity of AEs, laboratory parameters, and vital signs

Exploratory

- The biomarkers described in the SAP were:
  - Epidermal growth factor receptor (EGFR) gene copy number status (measured by fluorescence in situ hybridisation [FISH] and categorised as FISH+ [a high EGFR gene copy number], FISH- [a low EGFR gene copy number], or FISH unknown [no evaluable tumour sample])
  - EGFR protein expression status (categorised as EGFR+ [≥10% of cells staining for EGFR], EGFR- [<10% of cells staining for EGFR], or EGFR unknown [no evaluable tumour sample])
  - EGFR mutation status (categorised as M+ [mutation detected], M- [no mutation detected], or M unknown [no evaluable tumour sample])

  These biomarkers were investigated in relation to clinical efficacy (PFS, objective tumour response rate, and OS; their relationship with toxicity was only to be investigated in the event of an unexpected study result)

- Germline genetic factors (polymorphisms of pre-specified inheritable genes); this was optional and subject to additional patient consent (these data are to be reported separately)

- Changes in pain and fatigue as measured by the single items from the Physical Well-being section of the FACT-L

- Patient satisfaction questionnaire (UK only)

Statistical methods

As described in the SAP, the primary analysis compared PFS between gefitinib and vinorelbine using a proportional hazards model, which included various prognostic factors (gender, WHO performance status, histology, smoking history, disease stage, and racial origin). The hazard ratio (gefitinib:vinorelbine) was estimated, together with its associated 90% confidence interval (CI) and p-value;95% CIs for the hazard ratio are also presented, for comparison with the results of other studies. The analysis was performed on the intent-to-treat population (ITT).

Objective response rate was to be analysed using a logistic regression model (which allowed for the effect of treatment and included the same covariates as used in the primary analysis of PFS); the odds ratio and its associated 95% CI were to be estimated from the model. OS was analysed using a proportional hazards model (which allowed for the effect of treatment and included the same covariates as used in the primary analysis of PFS); the hazard ratio was estimated, together with its associated 95% CI. These efficacy analyses were performed on the ITT population.

Pulmonary symptom and QoL improvement rates were analysed in a similar way to objective response rate using the evaluable-for-PSI and evaluable-for-QoL populations (sub-sets of the ITT population), respectively.

If there were at least 20 events in the FISH+ or FISH- sub-groups, gefitinib:vinorelbine hazard ratios and 95% CIs were to be produced for that sub-group in the same way as for the analysis of PFS and OS for the overall population; a similar procedure was to be followed for EGFR expression and mutation. Efficacy comparisons between FISH sub-groups were also carried out for gefitinib and vinorelbine separately. There was no formal statistical analysis of the exploratory variables of changes in pain and fatigue or patient satisfaction – or any of the safety variables.

Patient population

In total, 196 patients from 41 centres in 10 countries were evaluated as part of the INVITE study (including 97 and 99 patients randomised to gefitinib and vinorelbine, respectively). The patients were representative of a chemonaïve, elderly population (mean age 75.1 years) with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. Tumours tended to be either squamous cell carcinoma (46.4%) or adenocarcinoma (40.3%), and more patients had metastatic (77.0%) than locally advanced (23.0%) disease. Approximately 16% of the

patients (31/196) were Asian. As might be expected in a small study, there were some small imbalances between the treatment groups in terms of demographic and other patient characteristics, but these were considered unlikely to have affected the interpretation of the results. The number of major protocol deviations was low (15 patients [7.7%]), suggesting that the study was conducted to high quality.

Efficacy and PRO results

The analyses were based on a data cut-off date of 24 February 2006. The results are as follows (note: hazard ratios of <1.00 and odds ratios of >1.00 indicate a favourable outcome for gefitinib compared with vinorelbine):

- Gefitinib was broadly similar to vinorelbine in terms of clinical efficacy (ITT population):
  - The hazard ratio for the comparison of PFS (primary outcome variable) between gefitinib (80.4% progressed) and vinorelbine (78.8% progressed) was 1.185 (90% CI 0.900 to 1.561; 95% CI 0.854 to 1.646; p=0.3095); there was a slight numerical advantage for vinorelbine but no statistically significant difference between the treatments.
  - Objective tumour responses (PRs) were achieved for 3/97 (3.1%) and 5/99 (5.1%) patients in the gefitinib and vinorelbine groups, respectively. Statistical analysis of objective response rate could not be performed due to the small number of responses.
  - The hazard ratio for the comparison of OS between gefitinib (53.6% dead) and vinorelbine (51.5% dead) was 0.984 (95% CI 0.660 to 1.467).
- Compliance and evaluability rates for the FACT-L and LCS were very good in both treatment groups: over the course of the study, compliance for completion of the FACT-L and LCS was >73% and >66%, respectively; the evaluability rate for both questionnaires was >93%.

  Consistent with the observed efficacy results, symptom improvement (PSI and LCS) rates appeared similar with gefitinib and vinorelbine:
  - The odds ratio for the comparison of PSI between gefitinib (32.6% improved) and vinorelbine (28.9% improved) was 1.016 (95% CI 0.373 to 2.766).
  - The odds ratio for the comparison of LCS between gefitinib (42.9% improved) and vinorelbine (39.1% improved) was 1.185 (95% CI 0.567 to 2.475).

  Consistent with the more favourable tolerability profile of gefitinib compared with vinorelbine (see below), overall QoL improvement (TOI and FACT-L) rates were higher with gefitinib than vinorelbine:

– The odds ratio for the comparison of TOI between gefitinib (22.9% improved) and vinorelbine (6.3% improved) was 5.467 (95% CI 1.610 to 18.559).

– The odds ratio for the comparison of FACT-L total score between gefitinib (24.3% improved) and vinorelbine (10.9% improved) was 2.966 (95% CI 1.055 to 8.336).

Safety results

The safety data reported here suggest that the tolerability profile of gefitinib – in terms of the type, frequency, and severity of AEs, laboratory parameters, and vital signs – was consistent with that seen in previously conducted monotherapy studies; it was manageable and compatible with the treatment of elderly patients with advanced NSCLC. AEs reported with vinorelbine in this study were consistent with the known safety profile of this cytotoxic treatment. The tolerability profile of gefitinib was favourable compared with vinorelbine in this first-line setting.

The majority of patients experienced at least one AE during the course of the study, and the overall incidence was slightly lower with gefitinib than vinorelbine. Table S1 presents an overview of the AEs reported.

Table S1 Number (%) of patients who had an AE in any category: EFS population

Category	Number (%) of patients[a]			
	Gefitinib N=94		Vinorelbine N=96	
Any AE	78	(83.0)	86	(89.6)
Any SAE	30	(31.9)	31	(32.3)
SAE leading to death	8	(8.5)	10	(10.4)
Any AE leading to discontinuation of treatment	12	(12.8)	21	(21.9)
Any CTC[b] grade 3 or 4 AE	35	(37.2)	51	(53.1)
Any CTC[b] grade 3, 4, or 5 AE	39	(41.5)	53	(55.2)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0
AE, Adverse event; EFS, Evaluable for safety; N, Number of patients; SAE, Serious AE.

- The most commonly reported AEs for gefitinib were diarrhoea (25.5%), rash (24.5%), and nausea (16.0%). The majority of these events were CTC grade 1 (mild) or 2 (moderate). This was generally consistent with the known toxicity profile of gefitinib.

- For vinorelbine, AEs of constipation (30.2%), fatigue (27.1%), neutropenia (24.0%), nausea (22.9%), and anorexia (20.8%) were frequently reported, and there

was a trend towards more severe AEs in the vinorelbine group. This was generally consistent with the known AE profile of this cytotoxic drug.

- Compared with vinorelbine, gefitinib was associated with a lower incidence and severity of blood disorders (anaemia, neutropenia, leukopenia, and febrile neutropenia), gastrointestinal disorders (constipation and nausea), fatigue/asthenia, vascular disorders (phlebitis/thrombophlebitis), peripheral oedema, and nervous system disorders (peripheral sensory neuropathy). Gefitinib was associated with a higher incidence of skin events (rash, dry skin, pruritus, acne, and rash pustular) and diarrhoea.

- The numbers of patients with an SAE with an outcome of death were low in both treatment groups (Table S1). No patients in the gefitinib group experienced treatment-related SAEs leading to death; 3 patients in the vinorelbine group died due to treatment-related events (pneumonia, neutropenic sepsis, and septic shock).

- Gefitinib was generally well tolerated. The frequency of dose interruptions due to AEs with gefitinib (9.6%) was less than the frequency of dose delays due to toxicity or AEs with vinorelbine (47.9%). In addition, fewer patients taking gefitinib (12.8%) discontinued study treatment due to AEs compared with vinorelbine (21.9%).

- OAEs were consistent with previous clinical studies and experience with gefitinib and vinorelbine; no new safety concerns were raised.

- The clinical laboratory results for gefitinib were similar to those seen in previous monotherapy studies; no new safety concerns were identified. As expected, deteriorations in haemoglobin, absolute neutrophil count, and white blood cell count were frequently observed with the cytotoxic vinorelbine. Gefitinib is not generally associated with haematological toxicity and only a small number of haematological laboratory abnormalities with gefitinib were reported in this study.

- No clinically relevant changes in vital signs and physical findings were evident with either gefitinib or vinorelbine.

Exploratory results

- The results of the exploratory evaluation of clinical efficacy in relation to EGFR gene copy number were unexpected given historical data, which showed superior survival for gefitinib-treated FISH+ patients compared with gefitinib-treated FISH- patients and similar survival for chemotherapy-treated FISH+ patients and FISH- patients:

  – For the sub-group of FISH+ patients (54 of 158 patients with known FISH status; 34.2%), vinorelbine-treated patients achieved better outcomes in terms

of PFS and OS than gefitinib-treated patients (hazard ratios were 3.125 [95% CI 1.446 to 6.756] for PFS and 2.878 [95% CI 1.212 to 6.832] for OS).

– Furthermore, gefitinib-treated FISH+ patients appeared to have worse PFS and OS than any other sub-group – including gefitinib-treated FISH- patients (FISH+:FISH- hazard ratios for gefitinib-treated patients were 1.310 [95% CI 0.773 to 2.220] for PFS and 1.614 [95% CI 0.867 to 3.006] for OS).

– There were no apparent imbalances in K-Ras mutation status (between FISH status sub-groups or between treatments) that were likely to have provided the explanation for the FISH results.

- The low numbers of patients with evaluable EGFR- (13/157 patients; 8.3%) or M+ (7/65 patients; 10.8%) tumour samples meant that meaningful evaluations of clinical efficacy in relation to EGFR protein expression and mutation status were not possible.

- Changes in pain and fatigue and patient satisfaction (UK patients only) appeared similar with gefitinib and vinorelbine.