Drug Product	IRESSA 250-mg tablet	**SYNOPSIS**	
Drug Substance	IRESSA (gefitinib, ZD1839)		
Study Code	D7913L00039		
Edition Number	1		
Date	18 March 2008		

A Randomised, Open-label, Parallel-group, Regional, Multicentre, Phase III Study of Oral Gefitinib (IRESSA®) versus Intravenous Docetaxel (TAXOTERE®) in Patients with Locally Advanced or Metastatic Recurrent Non-small Cell Lung Cancer who have Previously Received Platinum-based Chemotherapy

Prinicipal investigator

Professor Sang-We Kim MD PhD, Division of Oncology, Department of Medicine, Asan Medical Centre, University of Ulsan, Seoul, Korea

Study centre(s)

This study was conducted in 6 centres in Korea.

Publications

Study dates		**Phase of development**
First patient enrolled	5 September 2005	Therapeutic confirmatory (III)
Last patient enrolled	27 September 2006	
Data cut-off date	2 January 2007	

Objectives

The primary objective of this study was to compare progression free survival between patients on gefitinib or on docetaxel.

The secondary objectives of the study were to compare:

- overall objective tumor response rate (ORR) between patients on gefitinib or on docetaxel
- overall survival between patients on gefitinib or on docetaxel
- changes in quality of life (QoL) between patients on gefitinib or on docetaxel
- improvement in symptom control between patients on gefitinib or on docetaxel (for those patients who are symptomatic at baseline)
- safety and tolerability of gefitinib and docetaxel

Study design

This was a randomised, open-label, parallel-group, regional, multicentre, phase III study, designed to compare gefitinib (250 mg daily) with intravenous docetaxel (75 mg/m^2 3-weekly) in terms of progression free survival for patients with locally advanced or metastatic recurrent non-small cell lung cancer who have progressive or recurrent disease following prior platinum-based chemotherapy.

Target patient population and sample size

The target population was patients with locally advanced or metastatic NSCLC who had received prior platinum-based chemotherapy, had progressive or recurrent disease, and were now considered candidates for further chemotherapy with docetaxel.

150 patients were planned to be recruited to this trial and followed up until at least 120 progression events had occurred (estimated 6 months minimum). This number of events would provide 80% power to detect superiority of gefitinib to docetaxel at the 5% 1-sided significance level if the true underlying hazard ratio were 0.63 (estimated from the results of previous clinical studies where the median progression free survival time was 2.1-2.7 months for gefitinib 250mg and 1.5 months for docetaxel 75mg/m^2; and progression free survival rates at 5 months were 25-30% for gefitinib 250mg and 10-15% for docetaxel 75mg/m^2).

Patients were recruited by investigational sites in Korea with expertise in treating patients with NSCLC.

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

Gefitinib 250 mg, once daily in oral tablet form (one 250-mg tablet per dose), or docetaxel at 75 mg/m^2 every 3 weeks, intravenously over 1 hour. Commercially-available docetaxel (manufactured by Sanofi-Aventis) was supplied by the investigators' pharmacies.

Duration of treatment

Patients continued to receive treatment with either gefitinib or docetaxel until disease progression, unacceptable toxicity, withdrawal of consent or other specific criteria were reached. However, maximum duration of docetaxel administration should be 6 cycles in this study.

Criteria for evaluation (main variables)

Efficacy

Primary variable: PFS

Secondary variables: ORR, OS

Patient-reported outcomes (PROs)

Secondary variables: improvement in Quality of Life (QOL) as measured by Trial Outcome Index (TOI), and FACT-L total score. Disease-related symptoms were also to be evaluated by the Lung Cancer Subscale (LCS).

Safety

Secondary variables: frequency and severity of adverse events (AEs).

Statistical methods

The primary aim of this study was to compare PFS between gefitinib and docetaxel. The primary analysis population was the ITT population. A sensitivity analysis was performed in the PP population.

PFS was compared between the two treatment groups by an unadjusted analysis, using a log-rank test to produce a 1-sided p-value (consistent with the sample size calculation) and a producing a hazard ratio and 90% and 95% CIs from an unadjusted proportional hazards model; and by an adjusted analysis, using a proportional hazard model allowing for the effects of sex, histology (adenocarcinoma vs. other), smoking history (never smoked vs. ever smoked), and baseline performance status (0-1 vs 2), to produce a 1-sided p-value, hazard ratio and 90% and 95% CI. The unadjusted analysis in the ITT population at the 1-sided 5% significance level was the primary analysis. The 1-sided 5% significance level is equivalent to a conventional 2-sided 10% significance level. Hence a 90% CI is presented for the HR.

Objective tumour response rates, FACT-L total, TOI and LCS improvement rates were compared between the randomised treatment groups using chi-squared tests.

For overall survival, as follow-up is continuing, this is not the final analysis. At this interim stage, a hazard ratio and 95% confidence interval was calculated from an unadjusted proportional hazards model; however, this is merely for illustrative purposes as it was recognised that any analysis will be underpowered with so few events.

The planned interim analysis of this study after 50% of progression events had occurred was not performed, as rapid enrolment in the later stages of the study meant that this was due to occur very close the the final analysis. Hence no adjustments to significance levels at the final analysis were necessary.

Patient population

Consistent with the population intended by the protocol, patients who participated in this study were representative of an advanced pre-treated NSCLC population in Korea. A total of 161 patients were randomised to treatment (82 patients to receive gefitinib 250 mg and 79 patients to receive docetaxel); these patients were recruited from 6 centres in Korea and all had received prior platinum-based chemotherapy. All patients were second-line, (ie, had received one previous chemotherapy regimen) and 25.5% of patients had experienced a best response to their last chemotherapy of disease progression [PD]/unknown; 93.2% had WHO performance status 0, 1 and 67.7% had adenocarcinoma histology. In addition, 37.9% of patients were female and 41.0% were never smokers. The median age of the patients was 57 years (ranging from 20 to 74 years) (Table S1).

Table S1 Demography:ITT population

	Gefitinib (N=82)	Docetaxel (N=79)	Total (N=161)
Demographic		N (%)	
Sex			
Male	55 (67.1)	45 (57.0)	100 (62.1)
Female	27 (32.9)	34 (43.0)	61 (37.9)
		Mean±SD, Median, Minimum, Maximum	
Age(yr), (Median)	56.3±10.5, 57, 21, 74	56.1±11.4, 58, 20, 73	56.2±10.9, 57, 20, 74
18~29, (20.5)	2 (2.4)	2 (2.5)	4 (2.5)
30~39, (34)	4 (4.9)	5 (6.3)	9 (5.6)
40~49, (47)	11 (13.4)	12 (15.2)	23 (14.3)
50~59, (59)	31 (37.8)	25 (31.7)	56 (34.8)
60~69, (64)	29 (35.4)	30 (38.0)	59 (36.7)
70~79, (72.5)	5 (6.1)	5 (6.3)	10 (6.2)
Performance status (WHO)			
Normal Activity (PS 0)	2 (2.4)	3 (3.8)	5 (3.1)
Restricted Activity (PS 1)	74 (90.2)	71 (89.9)	145 (90.1)
In Bed <= 50% of the Time (PS 2)	6 (7.3)	5 (6.3)	11 (6.8)
Smoking			
Never smoked	30 (36.6)	36 (45.6)	66 (41.0)
Ex-smoker	51 (62.2)	43 (54.4)	94 (58.4)
Occasional smoker	0 (0.0)	0 (0.0)	0 (0.0)
Regular smoker	1 (1.2)	0 (0.0)	1 (0.6)
Histology Type			
Adeno	54 (65.9)	55 (69.6)	109 (67.7)
Squamous cell	17 (20.7)	11 (13.9)	28 (17.4)
Undifferentiated	7 (8.5)	9 (11.4)	16 (9.9)
Bronchoalveolar	1 (1.2)	0 (0.0)	1 (0.6)
Mixed squamous and adeno	1 (1.2)	1 (1.3)	2 (1.2)
Other	2 (2.4)	3 (3.8)	5 (3.1)
Best Response			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	28 (34.1)	30 (38.0)	58 (36.0)
SD	33 (40.2)	29 (36.7)	62 (38.5)
Progression	20 (24.4)	19 (24.1)	39 (24.2)
Unknown	0 (0.0)	1 (1.3)	1 (0.6)
Non-evaluable	1 (1.2)	0 (0.0)	1 (0.6)
Disease stage			
Locally advanced	11 (13.4)	14 (17.7)	25 (15.5)
Metastatic	71 (86.6)	65 (82.3)	136 (84.5)

The two treatment groups were generally well-balanced at baseline with respect to demographic factors, pre-study chemotherapy and disease characteristics, although there were slightly fewer females and never smokers in the gefitinib arm.

The study was conducted to high quality and in accordance with GCP.

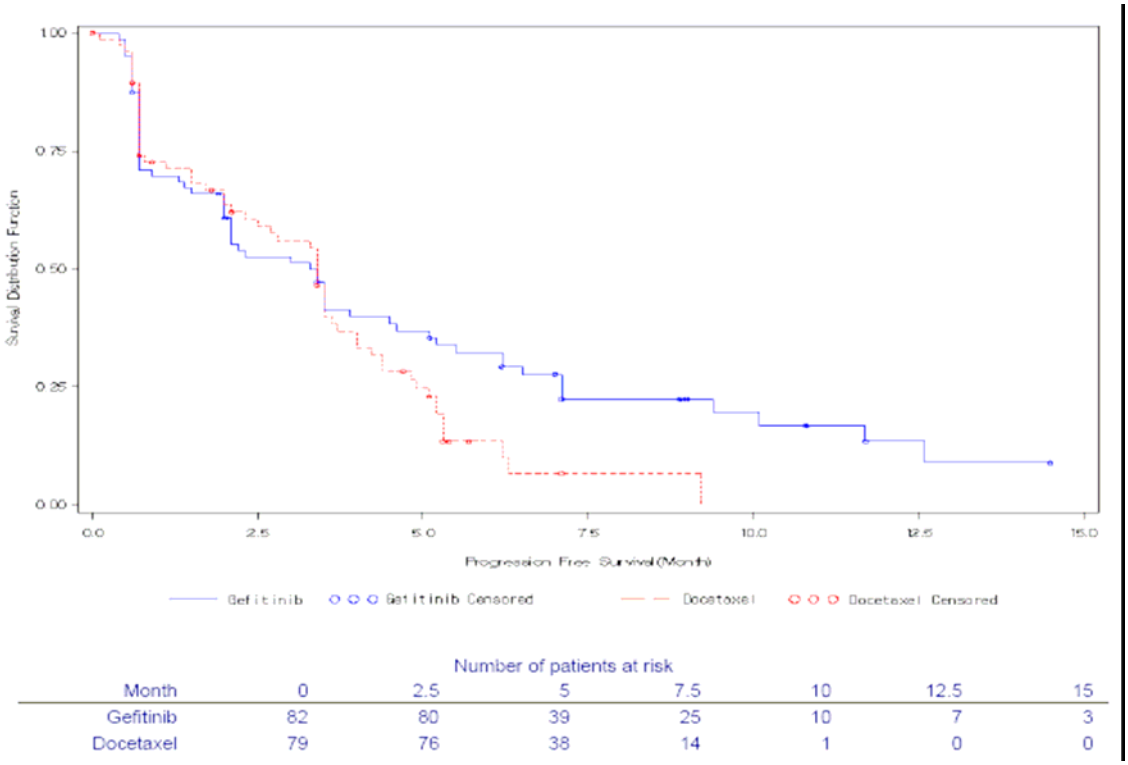
Efficacy results

Primary variable: Progression free survival

The analyses of progression free survival based on a data cut-off of 02 January 2007, by which time 120 disease progression events had occurred in the primary ITT population (74.5% maturity) indicate:

- Gefitinib had longer PFS than docetaxel (statistically significant at the pre-specified 1-sided 5% significance level) using the primary analysis unadjusted for covariates in the ITT population:
    - ITT PFS: Unadjusted HR (gefitinib:docetaxel) 0.729, 90% CI 0.533 to 0.998, 1-sided p=0.0441 (95% CI 0.502-1.060, 2-sided p=0.088) - (Figure S1)
- The secondary, supportive analysis of PFS adjusting for the effect of gender, histology, smoking history, WHO PS and disease stage supported and confirmed the primary PFS analysis:
    - ITT PFS: Adjusted HR 0.634, 90% CI 0.459 to 0.875, 1-sided p=0.0134 (95% CI 0.431-0.931, 2-sided p=0.027)
- Supportive analyses of PFS in the PP population were consistent with those in the ITT population:
    - PP PFS: Unadjusted HR 0.641, 90% CI 0.461 to 0.892, 1-sided p=0.0113 (95% CI 0.432-0.950, 2-sided p=0.023)
    - PP PFS: Adjusted HR 0.581, 90% CI 0.415 to 0.812, 1-sided p=0.0039 (95% CI 0.389-0.866, 2-sided p=0.008)

Figure S1 Progression free survival: ITT population



Number of patients at risk

Month	0	2.5	5	7.5	10	12.5	15
Gefitinib	82	80	39	25	10	7	3
Docetaxel	79	76	38	14	1	0	0

Secondary efficacy variables: Objective response rate, overall survival, and patient-reported outcomes:

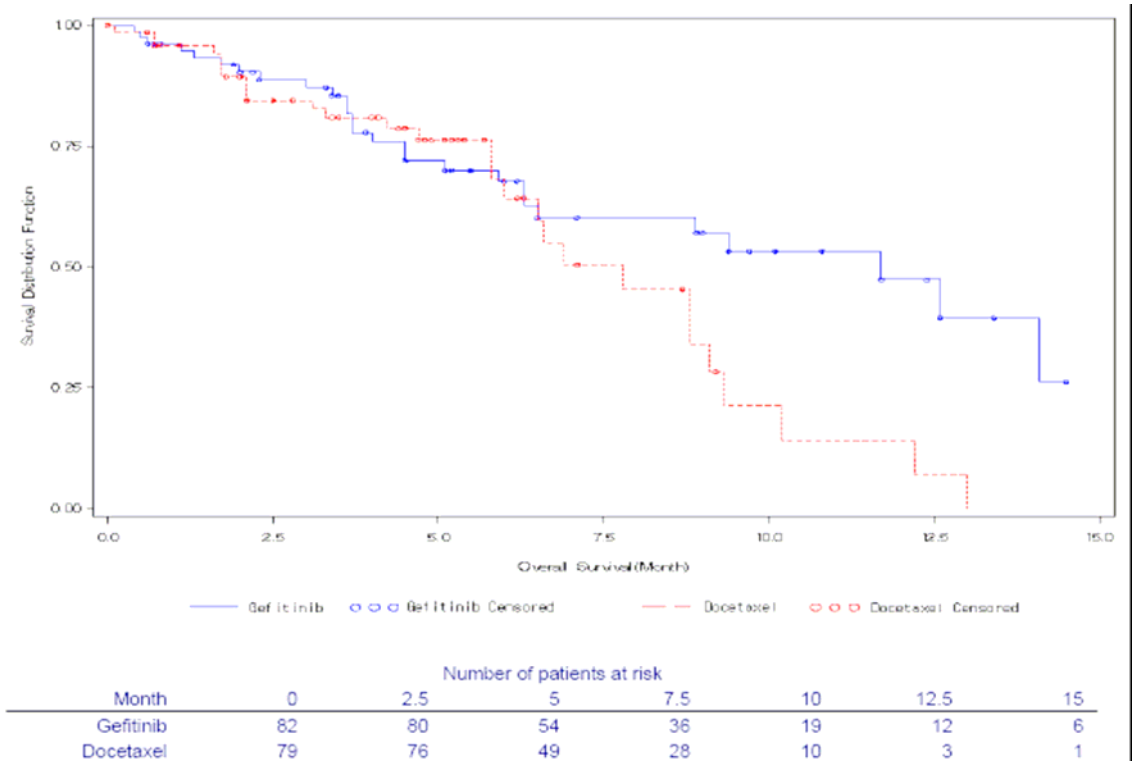
The study demonstrated superior efficacy for gefitinib compared to docetaxel for the secondary efficacy variable of objective response rate (ORR) in the overall ITT population, with consistent results in the supportive analysis in the PP population:

- ITT: ORR 28.1% with gefitinib versus 7.6% with docetaxel, 2-sided p=0.0007
- PP: ORR 29.0% with gefitinib versus 7.5% with docetaxel, 2-sided p=0.0011

At the data cut-off of 2 January 2007, 65.8% of all the ITT patients were still alive, 55 (67.1%) in gefitinib and 51 (64.6%) in docetaxel arm, while 27 (32.9%) gefitinib and 28 (35.4%) docetaxel patients had died. In this early look at overall survival (OS), gefitinib had numerically improved OS compared to docetaxel, although the number of events was small and the follow-up for survival is ongoing. Consistent results were seen in the PP population.

- ITT OS: Unadjusted HR 0.606, 95% CI 0.350 to 1.049 (Figure S2)
- PP OS: Unadjusted HR 0.486, 95% CI 0.275 to 0.861

Figure S2 Overall survival: ITT population



Number of patients at risk

Month	0	2.5	5	7.5	10	12.5	15
Gefitinib	82	80	54	36	19	12	6
Docetaxel	79	76	49	28	10	3	1

There were no statistically significant differences in terms of quality of life (QoL) or symptom improvement rates between the two treatments in the evaluable-for-QoL population (N=68 and N=66 patients in the gefitinib and docetaxel treatment groups, respectively).

.

- A similar proportion of patients on both arms had an improvement in the Functional Assessment of Cancer Therapy-Lung (FACT-L) Total Score (27.9% gefitinib versus 27.3% docetaxel, chi-squared test p=0.9310) and lung cancer symptom improvement (measured by the FACT-L Lung Cancer Subscale (LCS) - 39.7% gefitinib versus 37.9% docetaxel, p=0.8282).

- A numerically, but not statistically, greater proportion of patients experienced an improvement in QoL on gefitinib compared to docetaxel as measured by the Trial Outcome Index (TOI: 26.5% versus 13.6% respectively, chi-squared test p=0.0641).

Safety

The study safety data indicate that gefitinib 250 mg in advanced NSCLC has a favourable tolerability profile in terms of the type, frequency and severity of adverse events. Both gefitinib and docetaxel were generally well-tolerated and the AE profiles were consistent with their prescribing information.

Median time on treatment was 2.2 months (mean 3.8 months, range 0.3 to 15.4 months) for gefitinib 250 mg and 2.7 months (mean 2.5 months, range 0.1 to 4.6 months) for docetaxel 75 mg/m^2. The median number of docetaxel cycles was 3.5 (range 1 to 6), with 95.8% of all cycles given at the full dose.

Fewer dose modifications due to toxicity occurred with gefitinib (4.9% interruption) than with docetaxel (17.1% reduction/delay).

The key safety findings were:

There were fewer SAEs and CTC grade 3 or 4 AEs reported with gefitinib compared with docetaxel (Table S2).

Table S2 Categories of adverse events: Number (%) of patients who had at least 1 adverse event in any category (Evaluable for safety population)

Category[a]	Percentage of patients			
	Gefitinib 250 mg (N=81)		Docetaxel 75 mg/m^2 (N=76)	
Patients with an adverse event (AE)	79	(97.5)	72	(94.7)
CTC grade 3 or 4 AEs	17	(21.0)	21	(27.6)
Serious AEs	13	(16.0)	19	(25.0)
AE leading to discontinuation	6	(7.4)	7	(9.2)
SAE leading to death	4	(4.9)	2	(2.6)
Treatment-related[b] SAE leading to death	1	(1.2)	0	(0.0)

[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.

[b] Treatment-related adverse events were those events that the investigator considered to be possibly related to study treatment.

Adverse events

The AEs reported with gefitinib were generally consistent with its prescribing information (Table S3):

- The most commonly reported adverse events on the gefitinib arm were rash/acne, pruritus, anorexia, cough, diarrhoea and productive cough (Table S3); the majority of these events were CTC grade 1 (mild) or 2 (moderate).

AEs reported with docetaxel were generally consistent with the known safety profile of docetaxel (Table S3):

- The most commonly reported adverse events on the docetaxel arm were anorexia, alopecia, myalgia, asthenic conditions (including fatigue), cough, dyspnoea and neurotoxicity; the majority of these events were CTC grade 1 (mild) or 2 (moderate).

- Docetaxel patients experienced more CTC grade 3 or 4 neutropenia (absolute neutrophil count worsening from baseline to CTC grade 3 or 4 [gefitinib 1.3% vs docetaxel 6.6%].

    - Haematologic toxicity of docetaxel may not have been fully reflected in the data as the haematological nadir typically occurs several days into a cycle, but laboratory assessments were only scheduled for day 1 of each cycle.

Interstitial lung disease (ILD)-type adverse events were reported for both treatments (gefitinib 3 patients [3.7%] versus docetaxel 3 patients [3.9%]); 2 ILD events leading to death on gefitinib were reported (1 considered possibly treatment-related by the investigator).

Table S3 Most common adverse events (those occurring in at least 10% of patients in either treatment group): Evaluable for safety population

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib 250 mg (N=81)		Docetaxel 75 mg/m^2 (N=76)	
	All CTC grades	CTC grade 3/4	All CTC grades	CTC grade 3/4
Gastrointestinal disorders				
Diarrhoea	21(25.9)	1(1.2)	12(15.8)	0
Nausea	13(16.0)	0	14(18.4)	0
Constipation	9(11.1)	0	9(11.8)	0
Vomiting	4(4.9)	0	8(10.5)	0
Stomatitis*	3(3.7)	0	9(11.8)	1(1.3)
Dyspepsia	10 (12.3)	0	5 (6.6)	0
General disorders				
Asthenic conditions*	20(24.7)	1(1.2)	28(36.8)	3(3.9)
Chest pain	7(8.6)	0	12(15.8)	0
Pain	8(9.9)	2(2.5)	5(6.6)	0
Metabolism and nutrition disorders				
Anorexia*	29(35.8)	0	36(47.4)	2(2.6)
Musculoskeletal and connective tissue disorders				
Myalgia	4(4.9)	0	29(38.2)	0
Arthralgia	3(3.7)	0	9(11.8)	0
Nervous system disorders				
Neurotocixity*	17(21.0)	0	21(27.6)	0
Dizziness	9(11.1)	0	7(9.2)	0

Table S3 Most common adverse events (those occurring in at least 10% of patients in either treatment group): Evaluable for safety population

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib 250 mg (N=81)		Docetaxel 75 mg/m^2 (N=76)	
	All CTC grades	CTC grade 3/4	All CTC grades	CTC grade 3/4
Psychiatric disorders				
Insomnia	13(16.0)	0	18(23.7)	0
Respiratory, thoracic and mediastinal disorders				
Cough	25(30.9)	0	25(32.9)	0
Dyspnoea	20(24.7)	3(3.7)	21(27.6)	3(3.9)
Productive cough	21(25.9)	0	18(23.7)	0
Haemoptysis	9(11.1)	0	4(5.3)	0
Skin and subcutaneous disorders				
Rash/acnes*	61(75.3)	3(3.7)	6(7.9)	0
Pruritus*	40(49.4)	2(2.5)	5(6.6)	1(1.3)
Alopecia	4(4.9)	0	33(43.4)	0
Dry skin	12(14.8)	0	0	0
Nail and nail bed conditions*	2(2.5)	0	9(11.8)	0

* Grouped term – sum of several preferred terms

SAEs leading to death

The number of patients with SAEs leading to death was 4 (4.9%) for gefitinib (1 was considered possibly treatment-related) and 2 (2.6%) for docetaxel (Table S2).

- Gefitinib : 1 case of pneumonia, 1 case of septic shock and 2 cases of ILD
- Docetaxel: 1 case of pneumonia and 1 case of aspiration pneumonia

Overall Conclusions

This randomised, comparative study in patients with locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy demonstrates that:

- Progression free survival was longer with gefitinib compared to docetaxel.
  - Statistically significant at the pre-defined 1-sided 5% significance level (1-sided p=0.0441)
- Objective response rate was higher with gefitinib compared to docetaxel.
- An early analysis of overall survival suggests that survival may be longer with gefitinib compared docetaxel, but the number of events is small and follow-up is ongoing.

- Both gefitinib and docetaxel were generally well-tolerated and the AE profiles were consistent with their prescribing information.

- No significant differences in QoL or symptom improvement rates were seen with gefitinib compared to docetaxel.

Therefore, gefitinib 250 mg offers an important alternative to docetaxel 75 mg/m^2 that is effective and well-tolerated for patients in Korea with locally advanced or metastatic NSCLC who have received prior platinum-based chemotherapy and are considered candidates for further chemotherapy.