Abbreviated Clinical Study Report Synopsis	
Drug Substance	Gefitinib (IRESSA; ZD1839)
Study Code	D7913C00022
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A Phase I, Open-Label, Dose-Escalation Study Evaluating High-Dose Gefitinib (IRESSA®) on Weekly and Twice Weekly Schedules in Subjects with Solid Malignancies that are Locally Advanced, Recurrent or Metastatic

Study dates: First patient enrolled: 26 July 2005
Last patient completed: 04 January 2008

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

This study was conducted at two centres in the United States: Cedars-Sinai Medical Center/Louis Warschaw Prostate Cancer Center and Comprehensive Cancer Center/Desert Regional Medical Center. The first patient consented on 26 July 2005, and the last patient completed on 04 January 2008.

Publications

None at the time of writing this report.

Objectives and variables

Table S1 Study objectives and variables

Objective	Variable
Primary	
To determine the safety profile and maximum-tolerated dose (MTD)[a] of orally-administered escalating doses of gefitinib on a weekly and twice-weekly schedule in patients with solid malignancies that were locally advanced, recurrent, or metastatic	Adverse events (frequency and severity), ECGs, laboratory tests, physical examinations, and vital signs
Secondary	
To assess exposure to gefitinib at each dose level, and the linearity of that exposure across the doses during the progress of the study	Non compartmental derived values: maximum plasma (peak) drug concentration after single-dose administration (C_{max}); time to reach peak or maximum concentration (t_{max}); area under plasma concentration-time curve from zero to 24 h post dose ($AUC_{(0-24)}$); and minimum plasma (trough) drug concentration after repetitive dosing (C_{min})[b]
To characterize the population pharmacokinetics of gefitinib when given as either a once-weekly or twice-weekly schedule[c]	Total body clearance of drug from plasma at steady state, oral dose (CLss/f) and volume of distribution at steady state, oral dose (Vss/f) of gefitinib following administration of once weekly and twice weekly doses, with associated inter-subject variabilities. Individual empirical Bayesian derived C_{max}, area under plasma concentration-time curve from zero to infinity (AUC) and C_{min} values.
Exploratory	
To explore the activity of high-dose gefitinib and make a preliminary assessment of measurable and/or non-measurable disease tumour response within the different tumour types	Objective tumour response rate (ORR), time to tumour progression (TTP; hereafter referred to as progression-free survival [PFS]), disease-control rate (DCR)
To investigate the correlation of efficacy in patients treated with high-dose gefitinib with the expression of EGFR, HER-2, and other related biomarker status[d]	Efficacy (RR, TTP, DCR), EGFR and HER-2 expression and related biomarkers, gene expression profile, proteomics

[a] The MTD was not determined because this study was stopped after Cohort 7 (gefitinib 2000 mg dosed twice weekly) and before the MTD had been reached (due to the observation that gefitinib exposure did not increase with increasing dose; no safety issues were identified).

[b] Although not described in the Clinical Study Protocol, $AUC_{(0-168)}$ was also determined.

[c] The population pharmacokinetics were not characterised (early termination of the study resulted in a population of only 23 patients, which was considered too small for an effective population pharmacokinetic analysis).

[d] The biomarker analyses were not performed (a low number of samples was collected and from a variety of tumour types; it was felt unlikely that useful data could be generated from the analyses).

Study design

This was an open-label, phase-I, dose-escalation study. Sequential cohorts of patients were enrolled, beginning with Cohort 1 (gefitinib 1500 mg dosed weekly). It was planned to advance the cohorts, if possible, to Cohort 10 (gefitinib 3500 mg dosed twice weekly).

Target patient population and sample size

Patients with a histologically-confirmed solid tumour refractory to conventional treatment, or for which no standard treatment existed, were eligible to participate. Patients were aged ≥18 years, with a life expectancy of >12 weeks and WHO performance status <2.

No formal sample-size calculations were performed for this standard-design dose-escalation study. A maximum of 66 patients was expected to be required (n=3 to 6 per cohort, plus an additional cohort of six patients at the MTD to provide further safety information), although the number of patients was dependent on the number of dose escalations and the number of dose-limiting toxicities observed in each cohort.

Investigational product: dosage, mode of administration and batch numbers

The planned dose-escalation cohorts were:

- Cohorts 1 to 5: an oral dose of gefitinib (ZD1839) 1500 mg, 2000 mg, 2500 mg, 3000 mg and 3500 mg, respectively, on the first day of each week
- Cohorts 6 to 10: an oral dose of gefitinib (ZD1839) 1500 mg, 2000 mg, 2500 mg, 3000 mg and 3500 mg, respectively, on the first and fourth days of each week.

A Study Cohort Review Committee (comprising the Principal Investigators and members of the AstraZeneca study team) reviewed the safety and pharmacokinetic data upon completion of Cycle 1 (i.e. the first 28 days of study treatment) by all patients in each cohort, and provided authorization whether or not to advance to the next cohort.

Six batches of gefitinib were used in this study. For the gefitinib 100-mg tablets (F012651), batch numbers were 2000008984 (P/1427/24), 2000013561 (P/1520/22), and 2000016980 (P/1427/24). For the gefitinib 250-mg tablets (F012653), batch numbers were 2000008986 (P/1520/21), 2000015717 (P/1427/28), and 2000013579 (P/1427/25).

Duration of treatment

Each treatment cycle lasted 28 days. Patients were treated until disease progression or any other discontinuation criterion was met.

Statistical methods

No formal statistical hypothesis testing was planned in this study; descriptive statistics and graphical methods were used to summarise the data. Additional exploratory analyses were to be performed, if appropriate.

Patient population

Twenty-three patients were enrolled in Cohorts 1 to 7 (n=3 per cohort, except Cohorts 2 and 5 in which n=4). Although a maximum of ten sequential dose cohorts was planned, Cohort 7 (gefitinib 2000 mg twice weekly) was actually the final cohort (the study was stopped before the MTD had been reached due to the observation that gefitinib exposure did not increase with increasing dose; see below). No patient experienced a DLT during Cycle 1, and the majority of patients (87%) discontinued treatment due to disease progression. At the time of analysis, no patients were still receiving gefitinib. All enrolled patients were included in the pharmacokinetic, safety and efficacy analysis sets

Consistent with the population intended by the Clinical Study Protocol, patients who participated in this study were representative of a population with pre-treated, advanced solid malignancies. There was a wide variety of tumour types (most commonly adenocarcinoma [65% of patients]), and all patients had received at least one prior treatment regimen (65% of patients had received at least four prior regimens). Demographic and key baseline characteristics were reasonably well balanced between the two dose schedules (i.e. weekly and twice weekly). Small imbalances in patient characteristics due to chance are not unusual in a study of this size.

Summary of pharmacokinetic results

Evaluation of the individual gefitinib plasma concentration–time profiles for the first 24 hours post-dose (Figure S1), and the corresponding C_{max} and $AUC_{(0–24)}$ values, showed little difference in the exposure to gefitinib for doses increasing from 1500 mg to 3500 mg.

Individual $AUC_{(0–168)}$ data showed little difference in gefitinib exposure with increasing dose for weekly dosing (Figure S2). As expected, $AUC_{(0–168)}$ values for twice-weekly dosing (Figure S2) were increased over those for the same dose levels given weekly – but there was little difference between $AUC_{(0–168)}$ values for gefitinib 1500 mg and 2000 mg twice weekly, further confirming that there appears to be no increase in exposure for either dose schedule when increasing the dose from the starting dose of gefitinib 1500 mg.

Figure S1 **Individual gefitinib plasma concentration–time profiles following the first dose**

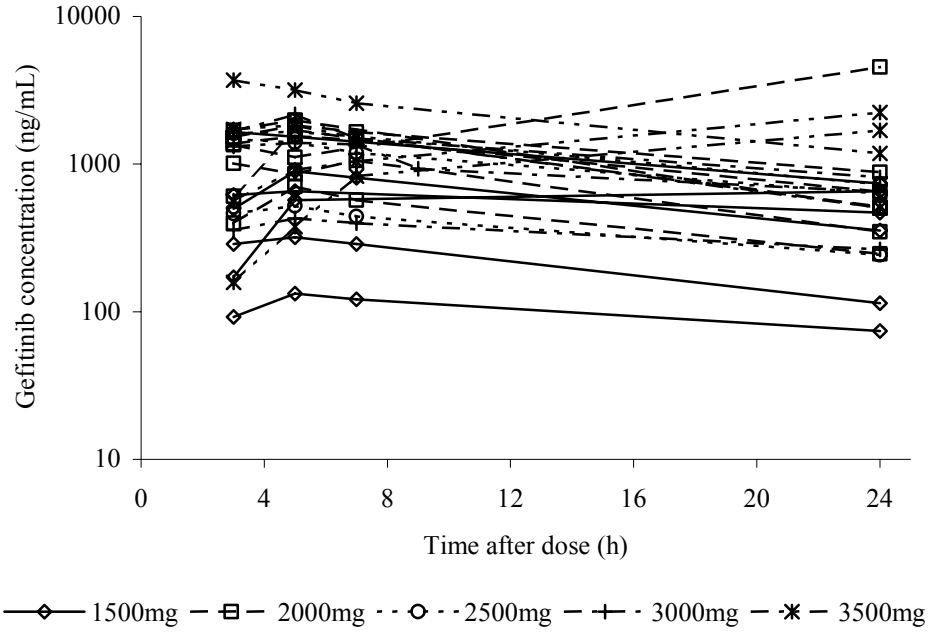
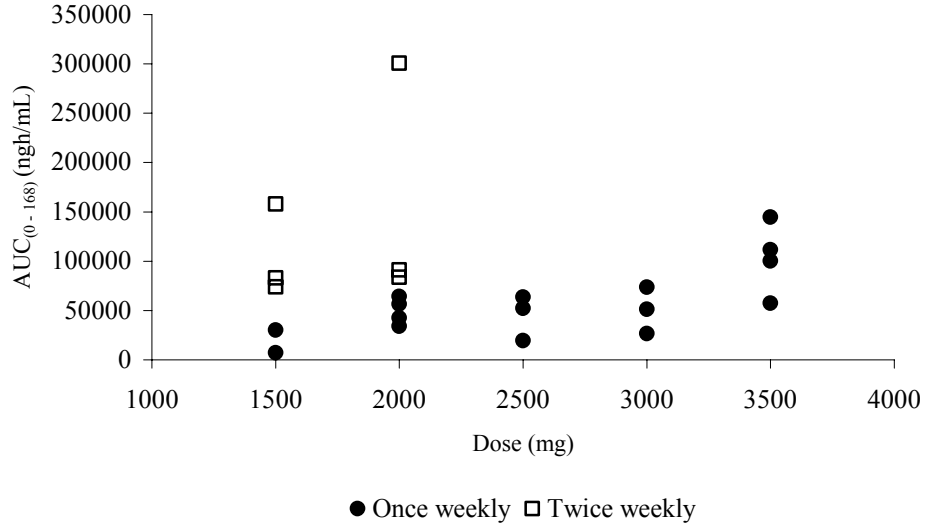


Figure S2 **Individual gefitinib $AUC_{(0–168)}$ values following the first dose**



Summary of safety results

Gefitinib was generally well tolerated in this study. No unexpected safety or tolerability concerns were identified, and early termination of the study was due entirely to the exposure findings. In light of the exposure findings, and coupled with the fact that there were small numbers of patients in each dose cohort, there was considered to be little value in presenting

the safety data separately for each cohort. Instead, the data are presented here for each dose schedule (i.e. weekly- and twice-weekly dosing) and also for all patients.

Most patients with AEs experienced events that were mild or moderate in severity (CTC Grades 1 or 2; Table S2), and most AEs were consistent with the known safety profile of gefitinib 250 mg/day (i.e. nausea, diarrhoea, vomiting, rash, and fatigue) or were related to co-morbidity. There were no AEs indicative of clinically relevant cardiac, renal or hepatic toxicity, and no ILD-type events. Although AEs in most patients were considered by the investigator to be possibly related to study medication (Table S2), this was unsurprising given the open-label nature of this study.

Table S2 Number (%) of patients who had an adverse event in any category: safety analysis set

Category[a]	N (%) of patients		
	Cohorts 1 to 5[b] Weekly schedule (n=17)	**Cohorts 6 and 7[c] Twice-weekly schedule (n=6)**	**All patients (N=23)**
All adverse events (AEs)	**15 (88.2)**	**6 (100.0)**	**21 (91.3)**
Treatment-related[d] AEs	14 (82.4)	6 (100.0)	20 (87.0)
All serious adverse events (SAEs)	**0**	**1 (16.7)**	**1 (4.3)**
Treatment-related[d] SAEs	0	0	0
Non-fatal SAEs	0	1 (16.7)	1 (4.3)
SAEs leading to death	0	0	0
AEs leading to discontinuation from study treatment	**0**	**1 (16.7)**	**1 (4.3)**
Treatment-related[d] AEs	0	0	0
SAEs	0	1 (16.7)	1 (4.3)
Treatment-related[d] SAEs	0	0	0
CTC[e] Grade 3 or 4 AEs	**3 (17.6)**	**2 (33.3)**	**5 (21.7)**
Treatment-related[d] CTC[e] Grade 3 or 4 AEs	1 (5.9)	0	1 (4.3)

[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] Gefitinib 1500 mg to 3500 mg dosed weekly.
[c] Gefitinib 1500 mg and 2000 mg dosed twice weekly.
[d] Treatment-related adverse events were those events that the investigator considered to be possibly related to study treatment.
[e] CTC Grade NCI version 3.0.
N/n Number of patients.

One patient in Cohort 6 (1500 mg twice weekly) experienced a non-fatal SAE: CTC Grade 4 cognitive disorder, which was considered by the investigator to be unrelated to study medication; this was the only AE that led to discontinuation from study treatment (Table S2).

Overall, the clinical laboratory results were similar to those seen in previous gefitinib (250 mg/day) monotherapy studies. No clinically relevant trends in vital signs or physical findings were evident. Of particular note is the lack of significant ECG findings with these high gefitinib doses: no patient had a QTc interval >500 ms during treatment.

The MTD could not be determined, because the study was stopped before the MTD had been reached.

Summary of efficacy results

There were no CRs and only one PR in this study (based on the investigator's assessment of response). The PR occurred in a 67-year-old male Caucasian patient with lung cancer; the patient, who was in Cohort 2 (2000 mg weekly), received his first dose of study treatment on 10 October 2005 and his last dose on 10 December 2005.