

## **Dose Escalation Study Design\*\***

### **Abstract**

#### *Purpose*

Previous studies established the safety of continuous gefitinib 250 or 500 mg daily. It was postulated that a higher dose may have increased efficacy by inhibiting signaling in both the mitogen-activated protein kinase and AKT pathways. This study investigated the tolerability, pharmacokinetics, and antitumor activity of high-dose gefitinib in patients with refractory solid malignancies.

#### *Methods*

Sequential cohorts received oral gefitinib once or twice-weekly, with dose escalation from 1,500 to 3,500 mg.

#### *Results*

Twenty-three patients received gefitinib at seven dose levels (1,500, 2,000, 2,500, 3,000, and 3,500 mg once-weekly; 1,500 and 2,000 mg twice-weekly). Gefitinib was well tolerated, with few dose-limiting toxicities. The maximum tolerated dose was determined to be 3,500 mg per week administered once-weekly. The most common gefitinib-related adverse events were nausea and diarrhea, vomiting, and rash. Pharmacokinetic data demonstrated no consistent increase in exposure to gefitinib with increasing dose across cohorts. Consequently, the study was considered completed early and gefitinib 2,000 mg twice-weekly was the highest dose administered. One of eight patients with non-small-cell lung cancer achieved a partial response.

#### *Conclusions*

Exposure to gefitinib did not increase consistently with increasing dose beyond gefitinib 1,500 mg once-weekly or twice-weekly. These data do not support further evaluation of gefitinib at high-dose schedules.

#### *Electronic supplementary material*

The online version of this article (doi:[10.1007/s00280-011-1757-y](https://doi.org/10.1007/s00280-011-1757-y)) contains supplementary material, which is available to authorized users.

**Keywords** Epidermal growth factor receptor – gefitinib – Pharmacokinetics – Solid tumors – Tyrosine kinase inhibitor

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## **Introduction**

Gefitinib is an orally active, small molecule inhibitor of the intracellular tyrosine kinase domain of the epidermal growth factor receptor (EGFR). Initial clinical studies with 250 or 500 mg continuous gefitinib monotherapy enrolled unselected populations of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) [1–4]. Subgroup analyses [2, 4–7] indicated that molecular markers had the potential to select for those patients most likely to

\*\*Dose Escalation Study adapted from Gross et al. published in *Cancer and Chemotherapy* on October 2011 (full reference on the last page). However, some of the data presented in this document is fictionalized for instructional purposes and are not intended to represent the actual study design or analysis.

benefit from treatment with gefitinib, with the presence of activating mutations in the *EGFR* gene shown to correlate with increased responsiveness to gefitinib [8–10].

In 2008, the phase III IRESSA Pan-Asia Study (IPASS) showed that the presence of an *EGFR* mutation was the strongest predictor of a better outcome in terms of progression-free survival (PFS) and response rate with first-line gefitinib compared with carboplatin/paclitaxel [11]. Two subsequent phase III studies have confirmed that first-line gefitinib improves PFS and response rate compared with doublet chemotherapy in patients with NSCLC selected for the presence of activating *EGFR* mutations [12, 13].

The current study was designed in early 2004, before *EGFR* mutations and their relationship with outcome to *EGFR* tyrosine kinase inhibitors (TKIs) had been reported, and the mechanisms determining sensitivity and resistance to gefitinib were not fully understood. One hypothesis was that signaling from *EGFR*/HER2 (erb-B2) or *EGFR*/HER3 heterodimers could be a mechanism by which some tumors are inherently resistant or acquire resistance to gefitinib [14]. Preclinical data indicated that signaling through both the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT pathways occurs in many tumors, and that blockade of both pathways by gefitinib is required for antitumor activity [15]. At the optimal biologic dose (250 mg/day), gefitinib was known to inhibit *EGFR* and MAPK phosphorylation signaling in skin [16]. However, in some models, higher concentrations of gefitinib were required to inhibit AKT activation [17]. Subsequently, the association between AKT activation and gefitinib sensitivity has also been demonstrated for activating *EGFR* mutations [8, 9, 18]. It was therefore postulated that a higher dose of gefitinib may have increased efficacy by inhibiting both the MAPK and AKT pathways. This phase I, dose-escalation study was performed to investigate the safety and tolerability of increasing doses of gefitinib in patients with locally advanced, recurrent, or metastatic solid malignancies.

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## Methods

### Study design

This open-label, phase I, dose-escalation study (ClinicalTrials.gov identifier NCT00127829) was conducted at one clinical center in the United States. The primary objective was to determine the safety profile and maximum tolerated dose (MTD) of gefitinib (IRESSA™, AstraZeneca, Macclesfield, UK) administered either once-weekly or twice-weekly in patients with locally advanced, recurrent, or metastatic solid malignancies. Secondary objectives included assessment of exposure to gefitinib at each dose level, and the linearity of exposure across doses. Antitumor activity was an exploratory objective.

### Patient eligibility

Eligible patients had histologically confirmed solid malignant tumors that were refractory to conventional treatment or for whom no standard treatment existed. Patients were aged  $\geq 18$  years, had a World Health Organization (WHO) performance status  $\leq 2$ , and a life expectancy of  $\geq 12$  weeks. Patients had a normal electrocardiogram with a QT interval corrected using Bazett's formula (QTc) of  $\leq 450$  ms; serum potassium  $\geq 3.7$  mEq/L; and adequate liver, renal, and bone marrow function (see Supplementary Appendix for additional eligibility requirements).

All patients gave written informed consent and the study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics. The final Clinical Study Protocol was approved by the Institutional Review Boards of the Cedars-Sinai Medical Center, and of the Comprehensive Cancer Center and Desert Regional Medical Center.

## Study design and treatment

Eligible patients were to be sequentially enrolled on escalating doses of oral gefitinib using a standard 3 + 3 design. Dosing started at gefitinib 1,500 mg administered once-weekly (days 1, 8, 15, and 22 of a 28-days cycle), with the dose increased at increments of 500 mg in sequential cohorts up to 3,500 mg (cohorts 1–5); subsequent sequential cohorts were to be administered the same dose of gefitinib (1,500, 2,000, 2,500, 3,000, 3,500 mg) on a twice-weekly basis (days 1 and 4, 8 and 11, 15 and 18, and 22 and 25 of a 28-days cycle; cohorts 6–10). Patients were instructed to take gefitinib promptly, in less than a 1-h period. As nausea and vomiting were commonly observed at the cohort 4 dose level (3,000 mg once-weekly), prophylactic antiemetic treatments were used for patients in cohort 5 and beyond.

Dose escalation was planned to proceed with cohorts of 3–6 patients enrolled at each dose level until the MTD was reached (see Online Resource). The MTD was considered to have been exceeded if two dose-limiting toxicities (DLTs) were observed in any cohort. An additional cohort of six patients was to be enrolled at the MTD. DLTs were defined as any of the following adverse events (AEs) determined to be possibly drug-related by the Study Cohort Review Committee: Common Toxicity Criteria (CTC) grade 4 skin toxicity; CTC grade 4 diarrhea or CTC grade 3 diarrhea that persisted at the same/higher grade for  $>4$  days despite aggressive antidiarrheal therapy; CTC grade 3 or 4 vomiting that persisted at the same/higher grade for  $>4$  days despite aggressive antiemetic therapy; CTC grade 3 or 4 central nervous system, lung, or renal toxicity, or elevation in liver transaminases or bilirubin lasting for  $>1$  week; QTc interval  $\geq 550$  ms; and any other CTC grade 3 or 4 event. Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal due to other reasons. Dose reductions/interruptions were permitted to manage gefitinib-related toxicity (see Online Resource).

## Safety assessments

WHO performance status, physical examination, vital signs, laboratory tests (hematology, blood biochemistry, blood coagulation), urinalysis, and concurrent medication were assessed at screening, at study visits, and at study discontinuation. Medical history, pregnancy testing (if applicable), and chest X-ray were also scheduled at screening. Cardiac monitoring was performed by 12-lead electrocardiogram (ECG) prior to any blood draws throughout cycle 1, every 12 weeks thereafter, and at discontinuation. The ECGs were evaluated and assessed for QT prolongation at each center by a local cardiologist. The procedures for patient management based on the QTc interval were as per European Union regulatory safety requirements. AEs were assessed throughout the study (CTC Version 3.0). A final follow-up assessment 30 days after study discontinuation included concurrent medication and AEs.

## Pharmacokinetic analyses

Blood samples for pharmacokinetic (PK) analysis were collected from each patient at 3, 5, and 7 h following gefitinib administration on day 1; 24 h post-dose (day 2), 72 h post-dose (day 4); and pre-dose on days 8, 15, and 22 in cycle 1 and pre-dose on day 1 in cycle 2. An additional sample was taken at 9 h post-dose on day 1 if an ECG was required at this time point (if ECGs at 3, 5, and 7 h post-dose had a QTc interval  $\geq 460$  ms that was trending upwards). Plasma concentrations of gefitinib were determined using liquid chromatography with tandem mass spectrometry [19] and PK parameters were calculated by standard methods.

## Efficacy assessments

Tumor response was assessed using response evaluation in solid tumors (RECIST) criteria. Patients with prostate cancer and ovarian cancer whose disease was nonmeasurable were followed by prostate-specific antigen level/bone scan and CA-125 level/computerized tomography scan, respectively. Efficacy assessments were repeated every 8 weeks (sooner if clinically indicated) and at the discontinuation visit (scans were only performed if the previous scan was  $>4$  weeks prior to the discontinuation visit).

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# Results

## Patients

Twenty-four patients were recruited (first patient enrolled July 2005, last patient completed January 2008), of whom 23 received treatment with gefitinib in cohorts 1–7 ( $n = 3$  per cohort except cohorts 2 and 5, where  $n = 4$ ) and were included in the safety, PK, and efficacy analyses.

✱ One patient (cohort 2) did not receive study treatment due to disease progression being noted following assignment but prior to the first dose and was excluded from the analyses. The median age of the study population was 67 years. Patients with a variety of solid tumor types were enrolled, with the most frequent being NSCLC and prostate cancer ( $n = 8$  each; Table 1). All patients had received at least one prior chemotherapy regimen, with the majority ( $n = 15$ ) receiving  $\geq 4$  prior chemotherapy regimens.

**Table 1 Patient demographics and baseline characteristics**

Characteristic	All treated patients (n = 23)
Male/female, n (%)	16 (69.6)/7 (30.4)
Median age (range), years	67 (36–82)
WHO performance status <sup>a</sup> , n (%)	
0	4 (17.4)
1	17 (73.9)
2	2 (8.7)
Tumor type, n (%)	
NSCLC	8 (34.8)
Prostate	8 (34.8)
Ovary	2 (8.7)
Other <sup>b</sup>	5 (21.7)
Number of prior chemotherapy regimens, n (%)	
1	4 (17.4)
2	2 (8.7)
3	2 (8.7)
≥4	15 (65.2)

NSCLC non-small-cell lung cancer, WHO World Health Organization

<sup>a</sup>World Health Organization (WHO) performance status is measured on a scale from 0 to 5, with 0 = Asymptomatic (Fully active, able to carry on all predisease activities without restriction) and 5 = Death

<sup>b</sup>Liver (n = 1), head and neck (n = 2), breast (n = 1), and pleural mesothelioma (n = 1)

All patients in cohort 4 experienced nausea and vomiting. The degree of nausea and vomiting in cohort 4 compared with previous cohorts (in cohort 3, two patients experienced nausea and one patient experienced vomiting), could not be attributed to increased gefitinib exposure, and was thought to be due to gefitinib only being available as 250 mg tablets, which resulted in patients consuming 6–14 tablets at one time (12 tablets in cohort 4). Therefore, beginning with cohort 5, patients received antiemetic therapy at the time of dosing and on subsequent days if needed (which improved medication tolerance overall), and took their tablets over a 1-h period.

Although a maximum of ten sequential dose cohorts was planned, the study was stopped after the enrollment of 24 patients in seven cohorts due to the observation that there was no consistent increase in exposure to gefitinib with increasing dose. No safety issues were identified. The highest dose given was gefitinib 2,000 mg twice-weekly (cohort 7), and the highest dose given once-weekly was 3,500 mg.

## Dose-limiting toxicity

No DLTs were observed during cycle 1 of the dose escalation at gefitinib 1,500, 2,000, 2,500, 3,000 mg once-weekly. One DLT (Grade 3 vomiting) was observed during cycle 2 of the dose escalation at gefitinib 3,500 mg once-weekly (cohort 5); one DLT (Grade 3 fatigue) was observed during cycle 1 of the 1,500 mg twice-weekly dose (cohort 6); and two DLTs (Grade 3 dyspepsia and Grade 4 hyperuricemia) were observed during cycle 2 of the 2,000 mg twice-weekly dose levels (cohort 7). Two DLTs at the 2,000 mg twice-weekly dose determined the MTD at 3,500 mg once-weekly.

## Tolerability

Median exposure to study treatment for the 23 patients evaluable for safety was 7.1 weeks (range 1.1–59.3 weeks). One patient in cohort 1 had a very long duration of treatment (~59 weeks) compared with the other patients (see “Efficacy”).

Gefitinib was generally well tolerated, with the spectrum of AEs consistent with the known tolerability profile of gefitinib 250 mg/day. All commonly reported AEs are shown in Table 2. Most patients (21 [91%]) experienced at least one AE, and most patients (20 [87%]) had at least one AE that was considered by the investigator to be possibly treatment-related. The most commonly reported treatment-related AEs were nausea and diarrhea (each occurred in 14 patients [61%]), vomiting (10 [44%]), and rash (7 [30%]). The majority of AEs were mild or moderate in severity (CTC grade 1 or 2). In total, CTC grade 3 or 4 AEs were reported by seven patients (one each in cohorts 1, 2, and 5; two in cohort 6; and four in cohort 7). Grade 3 AEs considered to be possibly treatment-related occurred in two patients, one each in cohorts 5, and 6 (vomiting and fatigue respectively). One grade 3 and one grade 4 AE considered to be possibly treatment-related occurred in one patient in cohort 7 (dyspepsia and hyperuricemia respectively). One patient in cohort 6 had a nonfatal serious AE (CTC grade 4 cognitive disorder), which was not considered treatment-related, but led to discontinuation from study treatment. Seven patients had died at the time of analysis, all due to disease progression. There was no evidence of clinically relevant cardiac, renal, or hepatic toxicity, and no interstitial lung disease-type events were reported. No ECG changes of any concern were observed: no patient’s QTc interval was “extremely prolonged” (>500 ms) either at baseline or during the study, and no patient met the predefined criteria to discontinue study treatment on the basis of prolonged QTc interval.

**Table 2** Total common adverse events occurring in the overall patient population and total grade 3/4 adverse events

Adverse event	Cohorts 1–5 <sup>a</sup>	Cohorts 6 and 7 <sup>b</sup>	All patients (n = 23)	
	Once-weekly schedule (n = 17)	Twice-weekly schedule (n = 6)	n	%
Nausea	12*	3	15	65.2

Adverse event	Cohorts 1–5 <sup>a</sup>	Cohorts 6 and 7 <sup>b</sup>	All patients (n = 23)	
	Once-weekly schedule (n = 17)	Twice-weekly schedule (n = 6)	n	%
Diarrhea	11*	4*	15	65.2
Vomiting	9*	3	12	52.2
Fatigue	6	2	8	34.8
Rash	5*	3*	8	34.8
Anorexia	3	1	4	17.4
Pain in extremity	2	2	4	17.4
Cough	2	2	4	17.4
Chills	2	1	3	13.0
Pyrexia	2	1	3	13.0
Urinary tract infection	3	0	3	13.0
Headache	2	1*	3	13.0
Dry skin	2	1	3	13.0
Pruritus	2	1	3	13.0
Total grade 3/4 serious adverse events <sup>c</sup>				
Bacteremia	1	—	1	4.3
Cognitive disorder	—	1 <sup>d</sup>	1	4.3
Dyspepsia	—	1*	1	4.3
Fatigue	—	1*	1	4.3
Hypocalcemia	—	1	1	4.3
Hyperuricemia	—	1 <sup>d,*</sup>	1	4.3
Pain in the extremity	—	1	1	4.3
Urinary tract infection	1	—	1	4.3
Vomiting	1*	—	1	4.3

Some or all reported adverse events determined to be possibly drug-related

<sup>a</sup>Gefitinib 1,500–3,500 mg dose once-weekly; Because plasma concentrations did not increase consistently with increasing dose, all once weekly regimens were grouped together for reporting safety

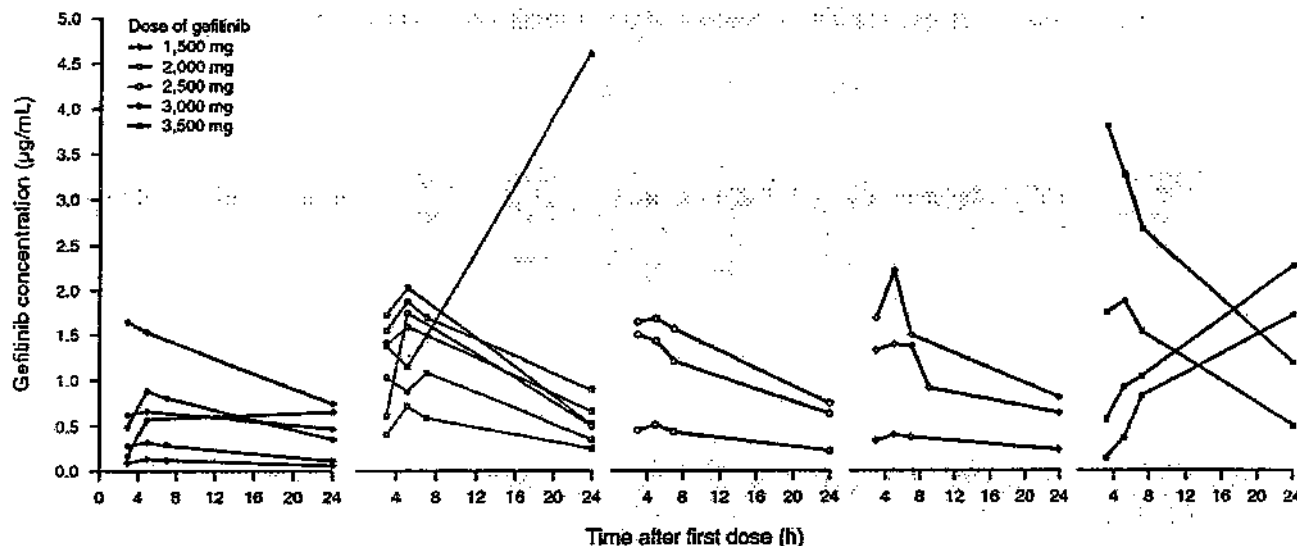
<sup>b</sup>Gefitinib 1,500 and 2,000 mg dose twice-weekly; Because plasma concentrations did not increase consistently with increasing dose, all twice weekly regimens were grouped together for reporting safety

<sup>c</sup>Patients may have experienced more than one different grade 3 or 4 adverse event

<sup>d</sup>Grade 4 adverse event

## Pharmacokinetics

Gefitinib plasma concentration versus time profiles are shown in Fig. 1 and the derived PK parameters are shown in Table 3.



**Fig. 1** Gefitinib plasma concentration versus time graphs following the first dose administered in the study

**Table 3** Derived pharmacokinetic parameters following the first dose (day 1) ( $n = 23$ )

Cohort	Gefitinib dose (mg)	No. of patients	Geometric mean (% CV) $C_{max}$ µg/mL	Geometric mean (% CV) $AUC_{0-24}$ µg h/mL	Geometric mean (% CV) $AUC_{0-168}$ µg h/mL	Median (range) $t_{max}$ h
Once-weekly						
1	1,500	3	0.336 (121)	5.41 (112)	NC	5 (5-5)
2	2,000	4	1.21 (44)	19.4 (52)	47.9 (29)	5 (5-7)
3	2,500	3	1.08 (71)	18.3 (66)	40.1 (71)	5 (3-5)
4	3,000	3	1.09 (101)	18.7 (73)	46.6 (55)	5 (5-5)
5	3,500	4	2.25 (36)	32.6 (31)	98.1 (41)	15 (3-24)
Twice-weekly						
6	1,500	3	0.892 (57)	17.0 (46)	99.0 (43)	5 (3-24)
7	2,000	3	2.48 (57)	34.5 (48)	132 (82)	5 (5-24)

$AUC_{0-24}$  area under the plasma-concentration curve from 0 to 24 h post-dose,  $AUC_{0-168}$  area under the plasma-concentration curve from 0 to 168 h post-dose,  $C_{max}$  maximum plasma gefitinib concentration, NC not calculated,  $t_{max}$  time to reach peak or maximum concentration

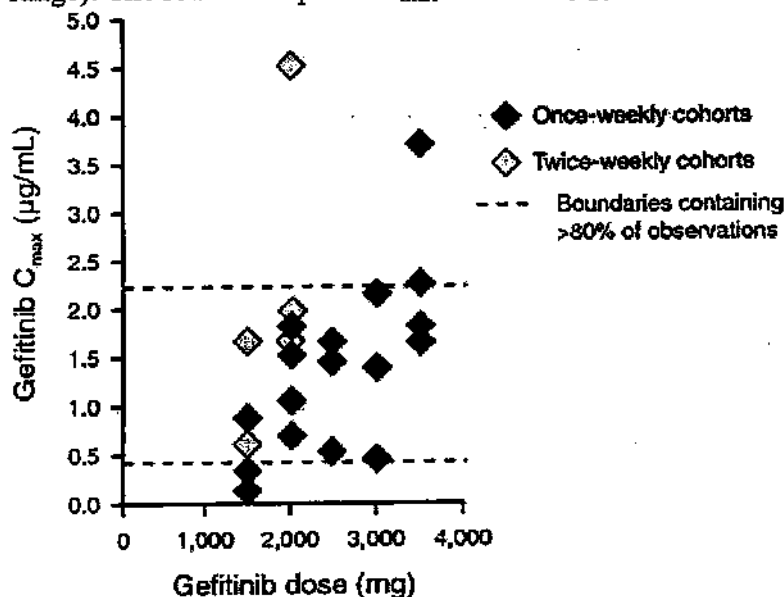
<sup>a</sup>Overall geometric mean across doses and regimens = 54.5 µg h/mL

In all dose cohorts, the absorption of gefitinib into the circulation was moderately slow. For most patients, highest concentrations were observed in the sample taken 5 h post-dose, although it



ranged from 3 h to as much as 24 h in a few patients. Time to reach peak or maximum concentration ( $t_{\max}$ ) appeared to be independent of dose. The plasma concentrations of gefitinib showed considerable inter-patient variation. However, with the exception of an increase from 1,500 to 2,000 mg and high concentrations in a few individual patients, the plasma concentrations did not seem to increase consistently with increasing dose.

Following the first administration in the patients who received gefitinib 1,500 mg once-weekly, the geometric mean (gmean) maximum plasma gefitinib concentration ( $C_{\max}$ ) was 0.34  $\mu\text{g/ml}$  and the area under the plasma-concentration curve from 0 to 24 h post-dose ( $\text{AUC}_{0-24}$ ) was 5.41  $\mu\text{g h/ml}$ . Variability among the three patients was high, with coefficients of variation exceeding 100%. Following the first 2,000 mg dose in cohort 2, the gmean  $C_{\max}$  and  $\text{AUC}_{0-24}$  were 3.6-fold higher, reaching 1.21  $\mu\text{g/ml}$  and 19.4  $\mu\text{g h/ml}$ , respectively. At 2,500 and 3,000 mg there was no further increase in gmean  $C_{\max}$  and  $\text{AUC}_{0-24}$ , although variability remained high with typically a 3–5-fold range between the lowest and highest values. Following the 3,500 mg dose, the gmean  $C_{\max}$  and  $\text{AUC}_{0-24}$  were raised slightly, but this was heavily influenced by high exposure in one patient. In the cohorts dosed twice-weekly, the gmean  $C_{\max}$  and  $\text{AUC}_{0-24}$  following the first dose were somewhat higher than when the same doses were given in the once-weekly regimen. However, the ranges of values were overlapping. Taken together across all doses, the individual  $C_{\max}$  values ( $n = 23$ ) fell within the range 0.43–2.17  $\mu\text{g/ml}$  and  $\text{AUC}_{0-24}$  values ( $n = 23$ ) within the range 9.19–33  $\mu\text{g h/ml}$  for all except four patients (two at 1,500 mg fell below the range and one at each of 2,000 mg twice-weekly and 3,500 mg were above the range). The relationships of  $C_{\max}$  and  $\text{AUC}_{0-24}$  with dose are displayed in Figs. 2 and 3.



**Fig. 2** Gefitinib  $C_{\max}$  versus dose for the first dose administered in the study.  $C_{\max}$  Maximum plasma gefitinib concentration

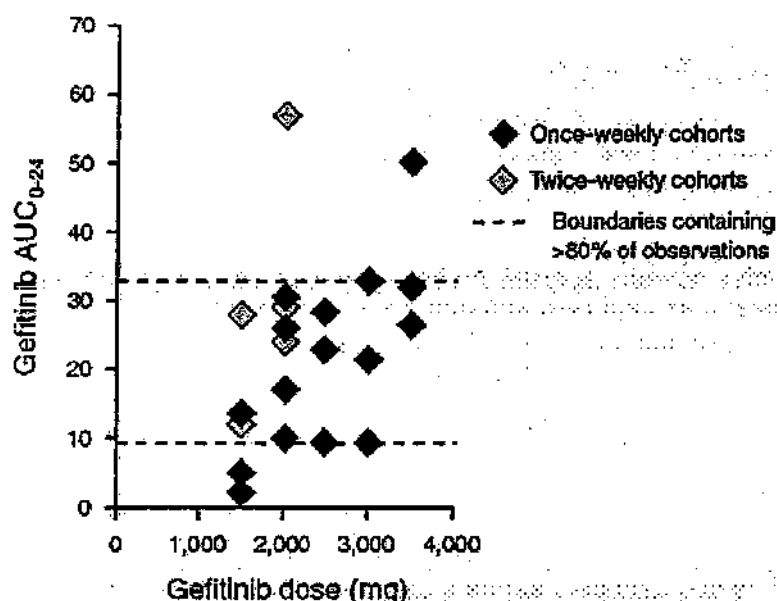


Fig. 3 Gefitinib AUC<sub>0-24</sub> versus dose for the first dose administered in the study. AUC<sub>0-24</sub> Area under the plasma-concentration curve from 0 to 24 h post-dose

Area under the plasma-concentration curve from 0 to 168 h post-dose (AUC<sub>0-168</sub>), a measure of exposure during the weekly treatment interval, showed a similar pattern to  $C_{max}$  and AUC<sub>0-24</sub>, with the majority of values falling within the range 19.4–100  $\mu\text{g h/ml}$ , irrespective of the weekly dose. As with the other PK parameters, a small number of individual patients had AUC<sub>0-168</sub> values either below this range (one at 1,500 mg) or above (one at 1,500 mg twice-weekly, two at 3,500 mg, and one at 2,000 mg twice-weekly).

## Efficacy

One patient who had NSCLC had a partial response, one patient who had head and neck cancer had stable disease, and 21 patients had progressive disease. The patient, who was classified with a best response of stable disease, met criteria for disease progression at day 250. However, they continued on treatment until day 417 due to investigator assessment of imaging data that was retrospectively determined to meet criteria for progressive disease.

## Discussion

This study demonstrated that there was no consistent increase in exposure to gefitinib, as measured in the blood, with increasing dose for either once-weekly or twice-weekly dosing schedules in patients with locally advanced, recurrent, or metastatic malignancies. This observation led to the early completion of the study. However, the MTD was reached and

determined to be 3,500 mg per week. The highest dose given was 2,000 mg twice-weekly, which was not well tolerated, with two DLTs observed.

Although the PK analysis reported here was limited by the small patient population, evaluation of the individual gefitinib plasma concentration versus time profiles and  $AUC_{0-24}$  showed little differentiation in exposure to gefitinib for doses increasing from 2,000 to 3,500 mg. The differences in mean exposure observed for once-weekly gefitinib 2,000 mg versus 1,500 mg probably represent increased absorption, whereas the similarity in exposure at the 2,000, 2,500, and 3,000 mg doses suggests a saturation of absorption. The increase in mean exposure at 3,500 mg versus 2,000, 2,500, and 3,000 mg is most likely attributable to the inter-patient variability. Although the inter-patient variability and small numbers of patients make assessment difficult, it does not appear that the vomiting in those patients administered gefitinib 3,000 mg markedly affected gefitinib exposure. The inter-patient variability in gefitinib exposure reported here is consistent with a previous study, in which inter-patient variability in gefitinib exposure was up to 8-fold at any given dose level [20].

Increased exposure ( $AUC_{0-168}$ ) was achieved by administration of 1,500 and 2,000 mg gefitinib twice-weekly but, with the exception of two patients, the exposures achieved were in the same range as the once-weekly values when scaled as mg gefitinib dosed per week.

Based on the assumption that  $AUC_{0-168}$  is unrelated to administered gefitinib dose, the overall mean  $AUC_{0-168}$  for the gefitinib high-dose schedules is 54.5  $\mu\text{g h/ml}$  (Table 3). This is similar to that reported for gefitinib 250 mg once-daily estimated from the mean steady-state trough concentration (43.7  $\mu\text{g h/ml}$ ) [21]. While this is an approximate comparison, it does indicate that on average it has not been possible to substantially exceed the exposure achieved with the registered dosage regimen. In individual patients, the exposures achieved, particularly using the twice-weekly dosage regimen, did appear to offer the promise of increased gefitinib exposure. However, these are probably still within the range of values expected from gefitinib 250 mg/day, given the known variability in gefitinib exposure. Moreover, it is unlikely that this higher exposure could be exploited clinically, as there are no known indicators that predict which patients will achieve high gefitinib exposure. Evaluation of the pharmacodynamics of gefitinib was not part of the current study, and we are not able to comment on how different dose levels affected the MAPK and AKT signaling pathways.

In agreement with our findings, a phase I trial of intermittent high-dose gefitinib on days 1 and 2 followed by docetaxel on day 3 of a 21-days cycle also found considerable overlap of gefitinib plasma concentrations between individual patients at different dose levels [22]. Although mean plasma levels of gefitinib increased with dose over the range 1,000–2,250 mg, an apparent saturation effect at gefitinib doses above 2,250 mg was observed.

Gefitinib was generally well tolerated in this study, with AEs consistent with the known tolerability profile of the recommended 250 mg daily dose of gefitinib [2, 4, 11]; early termination of the study was due entirely to the exposure findings. In view of the exposure data described above, it was not unexpected that the safety profile of the higher gefitinib doses was similar to that of 250 mg/day previously reported in the literature. Given that the study

population was heavily pretreated and refractory, and given the variety of tumors included, the low response rate (one partial response in a patient with NSCLC) is not surprising. Furthermore, *EGFR* mutation status was not evaluated as part of this study.

In conclusion, this study showed that exposure to gefitinib did not increase consistently with increasing dose beyond the starting dose of gefitinib 1,500 mg given either once-weekly or twice-weekly in patients with locally advanced, recurrent, or metastatic solid malignancies. There is considered to be no rationale to support further evaluation of gefitinib high-dose schedules.

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## Electronic supplementary material

Below is the link to the electronic supplementary material.

[Supplementary material 1 \(DOC 51 kb\)](#)

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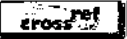


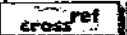

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**\*\*Dose Escalation Study adapted from the following Publication. However, some of the data presented in this document is fictionalized for instructional purposes.**

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## Clinical Trial Report

# Safety and pharmacokinetics of high-dose gefitinib in patients with solid tumors: results of a phase I study

Mitchell E. Gross<sup>1</sup>✉, Lawrence Leichman<sup>2</sup>, Elizabeth S. Lowe<sup>3</sup>, Alan Swaisland<sup>4,5</sup> and David B. Agus<sup>1</sup>

- (1) Center for Applied Molecular Medicine, University of Southern California Westside Cancer Center, Beverly Hills, CA, USA
- (2) Comprehensive Cancer Center and Desert Regional Medical Center, Palm Springs, CA, USA
- (3) AstraZeneca, Wilmington, DE, USA
- (4) AstraZeneca, Macclesfield, Cheshire, UK
- (5) *Present address:* TheraKin Consulting Ltd, Brereton, Sandbach, UK

✉ Mitchell E. Gross  
Email: [mitchell.gross@usc.edu](mailto:mitchell.gross@usc.edu)

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