Drug product:	IRESSA 250-mg tablet	**SYNOPSIS**	
Drug substance(s):	IRESSA (gefitinib, ZD1839)		
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A Phase III Randomised, Stratified, Parallel-group, Multi-centre, Comparative Study of Gefitinib (IRESSA®) 250 mg and 500 mg versus Methotrexate for Previously Treated Patients with Squamous Cell Carcinoma of the Head and Neck

International co-ordinating investigators

[redacted]

Study centre(s)

This study was conducted in 106 centres from 24 countries worldwide: Argentina (4), Australia (4), Belgium (5), Brazil (4),Canada (7), Czech Republic (6), Estonia (2), India (6), Italy (8), Israel (2), Greece (1), Latvia (1), Lithuania (2), Malaysia (2), Netherlands (4), Norway (1), Russia (5), Slovenia (1), Spain (7), South Africa (5), Sweden (3), Thailand (2), United Kingdom (2), United States of America (22).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	12 December 2003	Therapeutic confirmatory (III)
Last patient enrolled	24 January 2006	
Data cut-off	6 July 2006	

Objectives

The primary objective of this study was to compare gefitinib versus methotrexate in terms of overall survival.

The secondary objectives of the study were:

- to compare gefitinib (250 mg and 500 mg) versus methotrexate in terms of symptom improvement
- to compare gefitinib (250 mg and 500 mg) versus methotrexate in terms of overall objective tumour response (complete response [CR] plus partial response [PR]) using Response Evaluation Criteria in Solid Tumours (RECIST)
- to compare gefitinib (250 mg and 500 mg) versus methotrexate in terms of safety and tolerability
- to assess quality of life in patients treated with gefitinib (250 mg and 500 mg) versus methotrexate

The exploratory objectives of the study were:

- to determine steady-state plasma trough concentrations of gefitinib (250 mg and 500 mg)
- to investigate the correlation of the expression of biomarkers in tumour tissue obtained prior to study therapy with efficacy and tolerability and to determine a set of biomarkers to enable patient selection for therapy
- to investigate patient health status using the EuroQoL 5-dimension health status measure (EQ-5D) questionnaire

Prior to unblinding of the data, time to treatment failure was added as an exploratory variable to the analysis.

Study design

This was a Phase III randomised, stratified, partially-blinded, parallel-group, multi-centre, comparative study (D7919C00704, IMEX) comparing the efficacy and safety of gefitinib (IRESSA™ , ZD1839) 250 mg, gefitinib 500 mg, and methotrexate. Patients were stratified to either stratum A (patients had received a minimum of 2 cycles of platinum-based therapy for recurrent disease, with a response to the most recent course of progressive disease or stable disease) or stratum B (patients whose tumours had progressed after primary treatment and were considered by the investigator to be unsuitable to receive platinum-based chemotherapy).

Target subject population and sample size

Key inclusion criteria: Patients with histologically proven squamous cell carcinoma of the head and neck (SCCHN); aged ≥18 years; no prior anti-EGFR or methotrexate therapy; World Health Organisation (WHO) performance status 0, 1, or 2

- For patients in stratum A: Patients received radiotherapy or chemoradiotherapy as primary treatment and had a response to the most recent of a minimum of 2 courses of prior platinum therapy of progressive disease or stable disease

- For patients in stratum B: Patients whose tumours had progressed after primary treatment with radiotherapy or chemoradiotherapy and were unsuitable, as judged by the investigator, for platinum-based chemotherapy following failure of primary treatment

Key exclusion criteria: Patients with carcinoma of the post-nasal space, thyroid, sinus or salivary gland tumours; evidence of clinically active interstitial lung disease; presence of isolated recurrent disease that could be amenable to local therapy

Three hundred and eighty four cumulative deaths were required for the final analysis of survival. This study aimed to recruit 477 evaluable patients (159 patients per treatment arm).

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

Gefitinib 250 mg orally once daily, gefitinib 500 mg orally (2 x 250 mg tablet) once daily, or methotrexate 40 mg/m^2 administered intravenously on a weekly basis (with dose escalation to 60 mg/m^2 in the absence of toxicity). Formulation numbers were: gefitinib (given as 250 mg tablets) - [redacted]; placebo to match gefitinib - [redacted] Batch numbers can be found below[1].

Duration of treatment

Gefitinib was administered daily, and methotrexate administered weekly, until disease progression (objective disease progression or clinical progression) or discontinuation from the study for another reason.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: overall survival

- Secondary variable: objective tumour response (CR+PR)

- Exploratory variables: time to treatment failure (TTF), gefitinib (C_{min}) steady-state plasma concentrations, epidermal growth factor receptor (EGFR) protein expression, EGFR gene copy number, and human EGFR (HER2) gene copy number

[1] Gefitinib batch numbers: 10257F03, 10782F03, 10909G03, 11837J03, 12328G03, 13005J03, 22121I04, 94637J02, 21063J04, 21510C04, 93511A02, 92819B02, 93809J02, 10257F03, 10166J03, 12049K03, 90539A02, 91087E02, 92882F02. Placebo batch numbers: 12417I03, 22626B04, 12520J03, 22034A04, 92994B02, 91542K02, 8018H, 9025H.

Patient-reported outcomes (PROs)

- Secondary variables: Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) total score, Trial Outcome Index (TOI), FACT-H&N symptom index (FHNSI-10)

- Exploratory variable: patient health status (EQ-5D)

Safety

- Secondary variables: type, frequency, and severity of adverse events (AEs), laboratory parameters, vital signs

Statistical methods

The aim of the study was to detect superiority of gefitinib (250 mg or 500 mg) against methotrexate in terms of survival.

The primary analysis compared the overall survival (OS) of patients treated with gefitinib 250 mg or gefitinib 500 mg, to those treated with methotrexate. The primary analysis used a stratified log-rank test, with adjustment for randomisation stratification factor, and was carried out on the ITT population. Hochberg's procedure (Hochberg and Benjamini 1990) was to be employed to preserve the overall Type I error rate at 5%.

In a subsidiary analysis, time to death was also analysed by Cox's proportional hazards regression with adjustment for randomisation stratification factor (Stratum A or B). In addition, time to death was analysed by Cox's proportional hazards regression, with terms included to allow for the effects of randomised treatment and randomisation stratification factor, gender, race, performance status and disease status at baseline (locoregional vs metastatic).

Further supportive analyses based on the overall population were conducted comparing survival in the following pre-specified subgroups: stratum A vs stratum B, males vs females, asian racial origin vs, other race, current smoker (a little bit, somewhat, quite a bit, very much within the last 7 days at baseline) vs. non current smoker (not at all within the last 7 days at baseline) vs unknown (at baseline)[2], performance status (0,1 vs. 2,3), disease status at entry (local vs metastatic), primary site (oral cavity vs oropharynx vs larynx vs hypopharynx vs other).

Patient population

Four hundred and eighty six patients from 106 centres in 24 countries worldwide were evaluated (including 158, 167, and 161 patients randomised to gefitinib 250 mg, gefitinib

[2] The smoking status is taken from the FACT-H&N module. Patients were asked whether the question "I smoke cigarettes or other tobacco products" was true for them during the past 7 days

500 mg, and methotrexate, respectively). 256 (52.7%) patients were randomised to stratum A, and 230 (47.3%) patients randomised to stratum B.

As expected in a large randomised study with stratified randomisation, treatment groups were well balanced for all important prognostic factors, thus facilitating the interpretation of the treatment comparisons and enabling valid conclusions to be drawn from the study analyses. The patients recruited were typical of the broad population of previously treated patients with recurrent SCCHN.

Fifty three point five percent of patients were of performance status 1, and approximately 20% of patients were of performance status 2. The majority (394 [81.1%]) of patients had received previous chemotherapy, and almost all (479 [98.6%]) patients had received previous radiotherapy.

The original site of the primary cancer was the oral cavity for 155 (31.9%) patients, oropharynx for 123 (25.3%) patients, larynx for 118 (24.3%) patients, and hypopharynx for 55 (11.3%) patients. At diagnosis, 171 patients (35.2%) had T4 tumours, and approximately 25% of patients each had either T2 or T3 tumours. At diagnosis 175 (36.0%) patients had N0 tumours, 89 (18.3%) had N1 and 159 patients (32.7%) had N2 tumours. Most commonly at diagnosis, patients did not have distant metastases, with 430 patients (88.5%) having M0 disease at diagnosis.

At the time of study entry, the majority of patients had locoregional disease; 290 (59.7%) had locally recurrent disease, and 285 (58.6%) regional recurrences. 197 (40.5%) patients had metastatic disease at study entry.

Concomitant treatments were consistent with those to be expected to be prescribed to patients with SCCHN.

This trial was conducted to high quality; the number of major protocol deviations was low (5.6% of patients overall) with no imbalance across the treatment groups (gefitinib 250 mg: 14 [8.9%]; gefitinib 500 mg: 8 [4.8%]; methotrexate: 5 [3.1%]).

Efficacy and pharmacokinetic results

Primary variable: overall survival

- Neither gefitinib 250 mg nor 500 mg demonstrated an improvement in overall survival compared to methotrexate. There was a numerical advantage for methotrexate compared to gefitinib, although this did not reach statistical significance
  - Gefitinib 250 mg vs methotrexate: HR 1.22 (95% CI 0.95 to 1.57), p=0.1205, median overall survival 5.6 months vs 6.7 months
  - Gefitinib 500 mg vs methotrexate: HR 1.12 (95% CI 0.87 to 1.43), p=0.3899, median overall survival 6.0 months vs 6.7 months

- The one-year survival rates were 16.7%, 17.8%, and 26.5%, for the gefitinib 250 mg, gefitinib 500 mg, and methotrexate treatment arms, respectively
- The primary analysis was consistent with a supportive analysis using Cox's proportional hazards model with additional covariates
- There was no clear survival benefit in any of the pre-planned individual subgroup analyses

Secondary efficacy variables

- Objective responses were observed in all 3 treatment arms. In the gefitinib 250 mg arm 4 patients had a partial response (PR), in the gefitinib 500 mg arm 2 patients had a complete response (CR) and 10 had a PR. In the methotrexate arm, 1 patient had a CR, and 5 patients a PR
- The objective response rate appeared lower on gefitinib 250 mg than on methotrexate, although the comparison did not reach statistical significance (Odds ratio 1.45, 95% CL 0.40 to 5.26, p=0.5729; ORR 2.7% vs 3.9%)
- The objective response rate appeared higher on gefitinib 500 mg than on methotrexate, although the comparison did not reach statistical significance (Odds ratio 0.49, 95% CL 0.18 to 1.35, p=0.1650; ORR 7.6% vs 3.9%)
- Disease control rate (percentage of patients analysed with CR, PR or SD) was 50.3% in patients administered 250 mg gefitinib, 52.9% in patients administered 500 mg gefitinib, and 48.0% in patients administered methotrexate

Exploratory efficacy variable

- Gefitinib 250 mg and gefitinib 500 mg were both associated with a statistically significantly longer time to treatment failure compared to methotrexate
  - Gefitinib 250 mg vs methotrexate: HR 0.69 (95% CI 0.54 to 0.86), p=0.0013, median TTF 2.3 months vs 1.8 months
  - Gefitinib 500 mg vs methotrexate: HR 0.63 (95% CI 0.50 to 0.79), p<0.0001, median TTF 2.6 months vs 1.8 months

Key efficacy results are summarised in Table S1.

Table S1 Summary of key efficacy results: ITT population

Outcome variable	Hazard Ratio/Odds Ratio[a]	95% confidence interval	p-value
250 mg gefitinib (N=158) vs methotrexate (N=161)			
Overall survival[b]	1.22	0.95 to 1.57	0.1205

Table S1 Summary of key efficacy results: ITT population

Outcome variable	Hazard Ratio/Odds Ratio[a]	95% confidence interval	p-value
Objective response rate[c,d]	1.45	0.40 to 5.26	0.5729
Time to treatment failure[b,e]	0.69	0.54 to 0.86	0.0013
500 mg gefitinib (N=167) vs methotrexate (N=161)			
Overall survival[b]	1.12	0.87 to 1.43	0.3899
Objective response rate[c,d]	0.49	0.18 to 1.35	0.1650
Time to treatment failure[b,e]	0.63	0.50 to 0.79	<0.0001

[a] Hazard ratios/odds ratios of <1.00 show gefitinib has a favourable outcome compared to methotrexate
[b] Analysis performed using Stratified log-rank test with the following stratification factors included: randomisation stratification factor
[c] For objective response rate odds ratio is shown
[d] Analysis performed using stratified Mantel-Haenszel chi-squared test statistic, stratified by randomisation stratification factor, in evaluable for response population (N=147 250 mg gefitinib, N=157 500 mg gefitinib, N=152 methotrexate)
[e] Analysis performed as for overall survival, but in evaluable for response population
ITT, Intention to treat; N, Number of patients

Exploratory biomarker objective

Although the IMEX study was carried out in an unselected patient population, biomarker data was collected in order to try to identify those patients most likely, and least likely, to benefit from gefitinib treatment.

A positive EGFR expression status (referred to as EGFR+) was defined as having at least 10% of cells staining for EGFR (as in the ISEL study D7913C00709). Gene copy number per cell for both EGFR and HER2 were measured by fluorescence in situ hybridisation (FISH), according to a protocol described by Cappuzzo et al 2005. Patients were considered to have high EGFR gene copy number (referred to as EGFR FISH+) if they had high polysomy (≥4 copies in ≥40% of cells) or gene amplification (presence of tight EGFR gene clusters and a ratio of gene/chromosome per cell ≥2, or ≥15 copies of EGFR per cell in ≥10% of analysed cells). Other patients with an evaluable tumour sample were classed as low EGFR gene copy number (EGFR FISH-). Patients were considered to be of high HER2 gene copy number (referred to as HER2+) using the same criteria as described for EGFR gene copy number.

- 84 of the 212 patients with known EGFR FISH status were classified as EGFR FISH+ (39.6%)
- EGFR FISH+ patients did not appear to have longer survival than EGFR FISH- patients for any treatment arm
  - 250 mg gefitinib: EGFR FISH+ median survival 6.1 months (95% CI 4.5 to 7.9), EGFR FISH- median survival 6.0 months (95% CI 4.4 to 8.8)

  - 500 mg gefitinib: EGFR FISH+ median survival 5.9 months (95% CI 4.0 to 8.8), EGFR FISH- median survival 6.0 months (95% CI 4.6 to 8.6)

  - Methotrexate: EGFR FISH+ median survival 7.6 months (95% CI 6.0 to 9.9), EGFR FISH- median survival 6.8 months (95% CI 4.8 to 10.3)

- There was no significant difference in overall survival for EGFR FISH+ patients treated with gefitinib compared to those treated with methotrexate. A similar result was seen for EGFR FISH- patients

  - Gefitinib 250 mg vs methotrexate EGFR FISH+: HR 1.02, 95% CI 0.54 to 1.90, p=0.9590, median OS 6.1 months vs 7.6 months

  - Gefitinib 500 mg vs methotrexate EGFR FISH+: HR 1.30, 95% CI 0.71 to 2.37, p=0.3931, median OS 5.9 months vs 7.6 months

  - Overall survival treatment effects within the EGFR FISH+ and EGFR FISH- subgroups were similar to those seen in the overall population

- EGFR FISH+ patients treated with gefitinib appeared to have higher response rates, although the numbers of responses were small, and had statistically significantly longer TTF than those treated with methotrexate

  - ORR 250 mg gefitinib 3.57% (95% CI 0.09 to 18.35, 1 response in 28 patients), 500 mg gefitinib 13.79% (95% CI 3.89 to 31.67, 4 responses in 29 patients), methotrexate 0% (95% CI 0 to 12.21, 0 responses in 23 patients)

  - Gefitinib 250 mg vs methotrexate TTF: HR 0.31, 95% CI 0.16 to 0.59, p=0.0003, median TTF 3.6 months vs 1.9 months

  - Gefitinib 500 mg vs methotrexate TTF: HR 0.30, 95% CI 0.16 to 0.55, p=0.0001, median TTF 3.8 months vs 1.9 months

- EGFR FISH- patients treated with gefitinib did not appear to have better response rates and TTF compared to EGFR- patients treated with methotrexate

- Using the cut-off of 10%, all patients were EGFR positive apart from one. Therefore no further formal analyses were carried out

- HER2 gene copy number did not appear to predict for clinical outcome in patients with SCCHN across the three treatment arms

Secondary patient reported outcome variables: Quality of Life (FACT-H&N)

- Analysis of mean change from baseline score showed no statistically or clinically (as assessed from pre-specified criteria) significant differences between gefitinib and methotrexate for total FACT H&N or TOI changes

- The percentage of patients who experienced quality of life (QoL) improvement appeared higher for patients treated with gefitinib 250 mg than for patients treated with methotrexate as measured by the FACT-H&N total score (13.4% vs 6.0%) and TOI (11.3% vs 8.3%)

- The percentage of patients who experienced QoL improvement appeared higher for patients treated with gefitinib 500 mg than for patients treated with methotrexate as measured by the FACT-H&N total score (18.0% vs 6.0%) and TOI (18.9% vs 8.3%)

Secondary patient reported outcome variables: Symptoms (FHNSI-10)

- Analysis of mean change from baseline score showed that patients treated with gefitinib 500 mg had a statistically significant improvement in FHNSI-10, compared to patients treated with methotrexate. However this was not supported by the secondary worst case analysis. There was no significant difference for the comparison of gefitinib 250 mg and methotrexate arms. There were also no clinically significant differences (as assessed from pre-specified criteria) in symptom changes between gefitinib at either dose and methotrexate

- The percentage of patients who experienced symptom improvement appeared lower for patients treated with gefitinib 250 mg than for patients treated with methotrexate (14.4% vs 22.6%)

- The percentage of patients who experienced symptom improvement appeared higher for patients treated with gefitinib 500 mg than for patients treated with methotrexate (37.8% vs 22.6%)

Exploratory pharmacokinetic variables

- The pharmacokinetics reported in this study for patients with SCCHN treated with gefitinib, were similar to those seen in previous gefitinib monotherapy studies in patients with NSCLC

- There was an approximately 2-fold difference in the steady-state trough levels between the gefitinib 250 mg and 500 mg doses

- There was no difference in trough levels for concentrations of gefitinib at either dose between patients in stratum A and stratum B, nor was there any association between gefitinib exposure and objective response or EGFR gene copy number

- It appeared that exposure was slightly higher in patients administered gefitinib as a dispersion, compared to by tablet

Safety results

- The safety data reported here suggest that AEs and SAEs known to be associated with gefitinib were more frequent and of greater severity for patients receiving gefitinib 500 mg, compared to 250 mg, consistent with previous NSCLC studies. The observed safety profile in the head and neck patients receiving both doses of gefitinib was generally consistent with the known safety profile for gefitinib in NSCLC

- Gefitinib has been evaluated following patient exposure with a median duration of 71 days (250 mg) and 81 days (500 mg). Patients were generally exposed to gefitinib at either dose for longer periods (including interruptions) than patients were exposed to methotrexate (median exposure duration 58 days)

- The frequency of dose interruptions due to AEs for patients treated with gefitinib 250 mg and 500 mg was less than the frequency of dose reductions/delays for patients being treated with methotrexate (20.9%, 28.3% and 47.2% respectively experienced at least one interruption/delay or dose reduction to therapy). The proportion of patients withdrawing due to AEs was also less for patients being treated with gefitinib (250 mg and 500 mg) than for patients in the methotrexate treatment arm (8.2%, 7.8% and 13.8%, respectively)

- The majority of patients experienced one or more AEs. Similar numbers of patients in each treatment arm experienced AEs and SAEs

- The most common AEs reported for gefitinib in both 250 mg and 500 mg treatment arms were rash-type events and diarrhoea, and the majority of the events were mild to moderate (predominantly Common Terminology Criteria [CTC] grade 1 or 2). These events were in general consistent with the established safety profile for the drug

- The most common AEs reported for methotrexate were stomatitis and nausea, consistent with the established safety profile for the drug. The majority of the events of nausea were mild to moderate (CTC grade 1 or 2), but the events of stomatitis were CTC grade 3 or 4 for 16 patients (out of a total of 55 patients who had events of stomatitis), and resulted in withdrawal in 4 cases

- There were fewer treatment-related SAEs (1.9%, 5.4% and 15.1% respectively), and fewer treatment-related AEs of CTC grade 3, 4 or 5 (10.1%, 19.9% and 34.6%, respectively) reported for patients treated with gefitinib 250 mg and 500 mg than for those administered methotrexate

- A clinically significant difference in tumour haemorrhage-type events was observed between study treatment arms; 14 patients (8.9%) in the 250 mg gefitinib arm, 19 patients (11.4%) in the 500 mg gefitinib arm, and 3 patients (1.9%) in the methotrexate arm

- The majority of these tumour haemorrhage-type events were considered by the reporting physician to be mild to moderate in nature (CTC grades 1 and 2), and the majority resolved whilst study treatment continued

- Overall, 3 of the 36 patients died as a result of their tumour haemorrhage. All of the patients were receiving gefitinib treatment (2 on 250 mg, 1 on 500 mg). None of these 3 deaths were considered by the reporting physician to be causally related to gefitinib treatment

- Interstitial lung disease-type events were reported with similar frequency across the 3 arms; 2 patients (1.3%) on 250 mg gefitinib, 2 patients (1.2%) on 500 mg gefitinib and 2 patients (1.3%) on methotrexate

- The clinical laboratory results for gefitinib were similar to those seen in previous monotherapy studies in NSCLC. As expected from the known safety profile for methotrexate, a greater number of clinically significant haematological laboratory abnormalities were observed, compared to both doses of gefitinib. Gefitinib is not typically associated with these cytotoxic events. Deterioriations in liver enzymes were also seen with methotrexate, as expected

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

A summary of the safety data is shown in Table S2.

Table S2 Categories of adverse events: number (%) of patients who had at least 1 adverse event in any category (EFS population)

Category[a]	Number (%) of patients					
	Gefitinib 250 mg (N=158)		Gefitinib 500 mg (N=166)		Methotrexate (N=159)	
Patients with an AE	137	(86.7)	152	(91.6)	150	(94.3)
Treatment-related AEs	96	(60.8)	123	(74.1)	113	(71.1)
Serious AEs	43	(27.2)	48	(28.9)	51	(32.1)
Treatment-related SAEs	3	(1.9)	9	(5.4)	24	(15.1)
CTC Grade 3, 4 or 5 AEs	66	(41.8)	75	(45.2)	84	(52.8)
Treatment-related CTC Grade 3, 4 or 5 AE	16	(10.1)	33	(19.9)	55	(34.6)
AE leading to discontinuation	13	(8.2)	13	(7.8)	22	(13.8)
Treatment-related AEs leading to discontinuation	2	(1.3)	5	(3.0)	17	(10.7)
AE leading to death	13	(8.2)	8	(4.8)	11	(6.9)
Treatment-related AEs leading to death	1	(0.6)	0	(0)	4	(2.5)

[a] Patients may appear in more than one category of adverse event

AE, Adverse event; EFS, Evaluable for safety; N, Number of patients; SAE, Serious adverse event
Adverse events occurring during follow-up (ie occurring within 30 days after discontinuation of the investigational product) are included, adverse events occurring pre-study are not included

Conclusion(s)

[redacted]

- [redacted]

[redacted]

[redacted]

Date of the report

16 February 2007