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EJC Supplements Vol 2 No. 4 (2004) 34–39

EJC Supplements

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# New perspectives in the management of non-small cell lung cancer (NSCLC): Gefitinib (Iressa, ZD 1839)

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Received 19 September 2003; received in revised form 20 November 2003; accepted 28 November 2003

**Abstract**

Chemotherapy for first line treatment of advanced NSCLC is widely perceived to have reached a plateau in terms of efficacy. Therefore, it appears that the potential for improving current treatments by classical cytotoxid agents is limited, and novel therapies are urgently needed. One new promising therapeutic target is the epidermal growth factor receptor (EGFR). Gefitinib (IRESSA, ZD 1839), a small molecule EGFR-tyrosine kinase inhibitor is one of the most promising agents targeting EGFR. Several clinical phase I, II and II trials of Gefitinib of NSCLC have been carried out, and several trials are under way or planned to investigate and clarify the activity and toxicity of Gefitinib as second-line therapy, and to determine the benefits of single agent Gefitinib in various clinical settings for the treatment of early and late stage NSCLC. This review is to summarize the presently available clinical data and to illustrate Gefitinib's ongoing clinical development.


## 1. Introduction

Chemotherapy for first-line treatment of advanced Non-Small Cell Lung Cancer (NSCLC) is widely perceived to have reached a plateau in terms of efficacy. A recent study of several platinum-based doublet chemotherapy regimens failed to show a survival advantage for any of the regimens when compared with each other (Schiller and colleagues, 2002). Therefore, it appears that the potential for improving current treatments by classical cytotoxic agents is limited, and novel therapies are urgently needed. One new promising therapeutic target is the epidermal growth factor receptor (EGFR), whose activation has a major involvement in process essential for tumor growth, including proliferation, metastasis, and angiogenesis. Expression of EGFR has been shown to correlate with a poor prognosis, disease progression and resistance to chemotherapy (Wells, 2000). EGFR is i.e. targeted by the novel agent Gefitinib (Iressa, ZD 1839), a small-molecule EGFR tyrosine kinase inhibitor (EGFR-TKI). Gefitinib is an orally active agent, which blocks signal transduction pathways implicated in the proliferation and survival of cancer cells, in addition to host-dependent processes promoting cancer-cell growth. Several clinical phase I, II, and phase III trials of Gefitinib in NSCLC have been carried out or are underway. This review is to summarize the presently available clinical data and to illustrate Gefitinib's ongoing clinical development.

## 2. Phase I studies

The efficacy and tolerability of single agent Gefitinib have been investigated in four phase I dose-escalation studies involving a variety of solid tumors, including 100 patients with the diagnosis of advanced NSCLC [1–4].

Here, Gefitinib was well tolerated. The maximum tolerated dose was $\geqslant$700 mg/day. Diarrhea was dose-limiting at daily oral doses of 700–1000 mg. Acne-like rash, nausea, vomiting and asthenia were also noted. However, Getifinib did not cause myelosuppression, neuropathy, or significant alopecia. Pulmonary toxicity was not reported. Most of these adverse events where transient and mild in severity (CTC grade I or II). The incidence and severity of Gefitinib related adverse events generally increased as the dose increased.

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doi:10.1016/j.ejcsup.2003.11.002

Gefitinib exhibited encouraging antitumor activity at a range of dose levels. Responses were seen across the dose range 150–700 mg/day, with no clear dose-response relationship. Despite inter-patient variability in exposure, biologically relevant plasma concentrations (exposure levels well above the inhibitory concentration that causes 90% inhibition [$IC_{90}$] for KB oral carcinoma cells) were maintained at the doses of 150 mg/day and above. Fixed doses of 250 and 500 mg/day were therefore selected for subsequent phase II and III studies: 250 mg/day is higher than the lowest dose level at which objective tumor regression was seen, while 500 mg/day is the highest dose that was well tolerated when taken continuously in phase I trials.

In addition, two phase I studies were undertaken to examine the effect of adding Gefitinib (250 mg and 500 mg once daily) to two different standard cytotoxic doublet chemotherapy regimens commonly used in the first-line treatment of NSCLC [5,6]. In a study that combined Gefitinib with Carboplatin and Paclitaxel in 24 chemotherapy-naïve patients it was shown that this combination was well tolerated, with no new, increased, or cumulative toxicity or clinically relevant pharmacokinetic interactions. The trial was conducted in two parts. Initially (part 1) patients were randomly assigned to receive intermittent Gefitinib with cycle 1 or 2 of chemotherapy. Thereafter (part 2), the highest dose of Gefitinib that was given without dose-limiting toxicity from part 1 was administered continuously beginning with the first cycle of chemotherapy. Three sequentially enrolled cohorts received Gefitinib 250 and 500 mg (intermittently) and 500 mg (continuously). On the continuous Gefitinib schedule, one of nine patients experienced a grade III pneumonia, which was believed unlikely to be caused by Gefitinib therapy and occurred after the fifth cycle of chemotherapy. Five confirmed partial responses were observed (21%; 95% CI: 9 to 40). The medium duration of responses was five month. Furthermore, two more patients had an unconfirmed partial response, nine patients had stable disease, and three patients had progression. One of the documented responders was a woman with brain and wide spread bone metastasis.

In the second study Gefitinib was combined with Cisplatin and Gemcitabine in 18 chemotherapy-naive patients. Here, Gefitinib did not appeared to increase the overall toxicity of cytotoxic agents. The pharmacokinetic data showed that this combination had no clinically significant effects on the exposure to Gefitinib, Cisplatin, or Gemcitabine. The activity data were promising. Of 17 evaluable patients, nine (five NSCLC) had a partial response and seven (four NSCLC) had disease stabilization.

## 3. Randomized phase II studies

So far Gefitinib's clinical development has concentrated on advanced NSCLC and efficacy and toxicity data for second and first-line therapy using Gefitinib as single agent or in combination with standard doublet-chemotherapy have recently been released.

*Gefitinib for chemotherapy pre-treated patients having advanced NSCLC (2rd/3rd-line or more) (IDEAL-trials: Iressa Dose Evaluation in Advanced Lung cancer):* Two randomized, double-blind phase II trials investigated tumor response, disease related symptom response, and safety of daily oral Gefitinib (250 versus 500 mg/day) [7,8] (Fig. 1). Patients treated had locally advanced or metastatic NSCLC and had failed one, two or more prior chemotherapy regimens containing platinum and/or Docetaxel. More than 400 patients were randomized. The medium age was 60–62 years. Most of the patients had a performance status of 0–1, histologically an adeno-carcinoma (bronchiolo-alveolar carcinoma were included) and no tumor induced symptoms at entry. Patients with stable brain metastasis were not excluded. Tumor response rates (partial remissions) for the 250 mg (17.5%; 12%) and 500 mg (18.1%; 9.0%) were similar and did not show any statistical difference in both studies (Fig. 2). In the international study (IDEAL 1) the response rate was higher for Japanese than non-Japanese (27.5% versus 10.4%; $P = 0.0023$). This statistically significant difference could not be explained by pharmacokinetic differences. However, baseline prognostic factors such as performance status

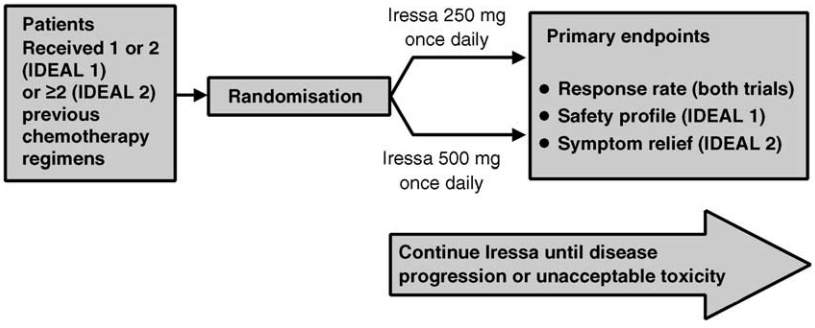


Fig. 1. Iressa as 2nd/3rd-line therapy for advanced NSCLC: phase II—study results [7,8].

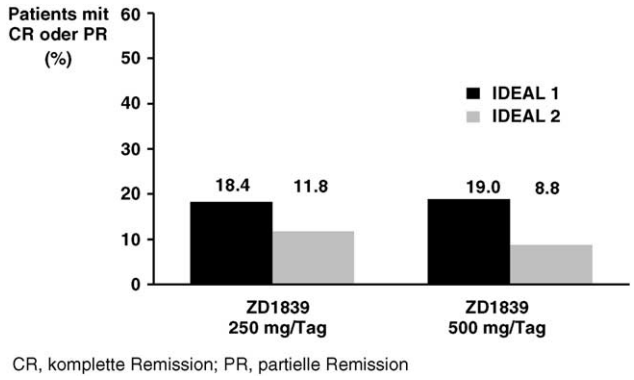


Fig. 2. Iressa as 2nd/3rd-line therapy for advanced NSCLC: phase II—study results [7,8].

0–1, female gender, and adeno-carcinoma were identified that accounts for the results. In the American multicenter study (IDEAL 2) symptom improvement and radiographic response were observed in all subgroups. However, a multivariable comparison (which included gender, histologic subtype, performance status, age, number of prior regimens, and months for initial diagnosis) demonstrated only female gender to be predictive of response both for symptom improvement and radiographic regression. In addition, it also have been reported that both patients who never smoked cigarettes and those with bronchiolo-alveolar carcinoma are more likely to respond to Gefitinib therapy [9]. These observations may help to increase the understanding of Gefitinib's mechanism of action and its correlation to tumor regression, but at this time should not be routinely used to select patients to receive Gefitinib therapy or not. Symptom assessment were measured using the Fact-L instrument [10,11]. Seven symptoms were recorded weekly in presents and severity using the lung cancer subscale (LCS): shortness of breath, weight loss, clarity of thinking, cough, appetite, chest tightness, and difficulty breathing.

Symptom response rates were about 40% with no difference between 250 and 500 mg/day. Approximately 60% of patients who experienced symptom response did so by the second week of treatment. Improvement in disease-related symptoms was associated with objective tumor responses and an increase in medium progression-free and overall survival. Medium survival was about 7 months in both studies for the two doses. Adverse events were generally mild, fewer patients on 250 mg experienced drug related toxicity grade 3/4 or withdrawals compared with 500 mg. Most common were grade 1/2 diarrhea and skin disorders, including rash, pruritus, dry skin, and acne-like changes. Patients with rash also frequently reported other skin-related symptoms. The rash appeared on the face, neck, and trunk, and commonly disappeared or improved despite continuing therapy. In the majority of patients it occurred during the first treatment cycle. Also the majority of patients who responded to Gefitinib therapy developed some kind of skin toxicity, the majority of those who did not show any objective tumor regression also experienced skin toxicity. Lung toxicity was uncommon in both studies. Two patients on the 500 mg/day dose of Gefitinib experienced an interstitial lung-disease-type events (interstitial pneumonia and pneumonitis) in the international trial. In the American study pulmonary events (i.e. pneumonia, aspiration, respiratory distress syndrome) were noted in 13 patients receiving 250 mg of Gefitinib and in 14 patients receiving 500 mg. Non of the pulmonary events were considered drug-related by the investigators.

Therefore it can be concluded that Gefitinib single agent used in chemotherapeutically pretreated patients (second/third-line therapy) provides durable clinically meaningful antitumor activity, rapid significant and clinically meaningful symptom relief and improvement in quality of life (Natale and colleagues, 2002; Douillard and colleagues, 2002). Gefitinib 250 mg has comparable efficacy but a more favorable safety profile and better tolerability than 500 mg/day. The data support Gefitinib 250 mg as an important novel treatment option for patients with chemotherapy-pretreated advanced NSCLC.

## 4. Randomized phase III studies

*Gefitinib in combination with standard chemotherapy in chemotherapy-naive patients (first-line) (Intact-trials: Iressa NSCLC Trial Assessing Combination Therapy):* Because of encouraging phase I data, Gemcitabine/Cisplatin (INTACT 1) and Taxol/Carboplatin (INTACT

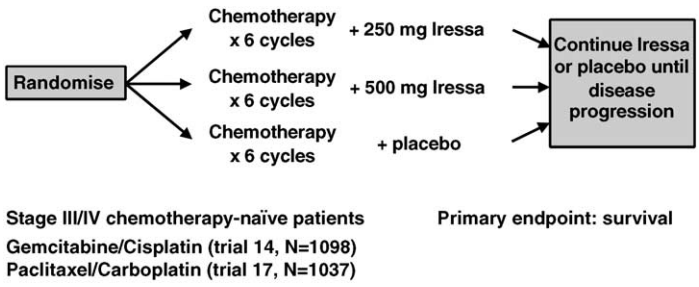


Fig. 3. Gefitinib (Iressa, ZD 1839) combination therapy in NSCLC: phase III trials [12,13].

2) were assessed in two randomized, double-blind, placebo-controlled, multicenter trials (Fig. 3). Chemotherapy-naive patients with stage III/IV disease, performance status 0–2 and, age ⩾18 years were randomized to chemotherapy plus placebo, chemotherapy plus 250 mg/day or chemotherapy plus 500 mg/day Gefitinib. Chemotherapy consisted of six cycles. Treatment with Gefitinib or placebo could be continued until disease progression. The primary endpoint was overall survival, secondary endpoints were progression-free survival and time to worsening of symptoms as assessed by the lung cancer subscale (LCS) of the FACT-L questionnaire. Other endpoints included symptom improvement, objective tumour response, disease control rate (CR/PR/SD), quality of life, and safety. A total of more than 2000 patients were recruited (medium age 61 years, performance status of 0–1 in about 2/3 of the patients, stage IV disease in about 70%). The three treatment groups were well balanced across all disease and demographic characteristics. There were no statistically significant differences in overall survival (Fig. 4), progression-free survival and time to worsening of symptoms across the treatment arms in both studies [12,13].

Subsequent subset analysis of the INTACT data by an univariat model or a multivariat analysis have recently been performed [14,15] in order to identify any survival benefit for certain patient characteristics (i.e. performance status, tumor stage, weight loss, pattern of metastases, gender, histology). However, there was no survival advantage in any of the subgroups when Gefitinib at any dose was added to standard chemotherapy.

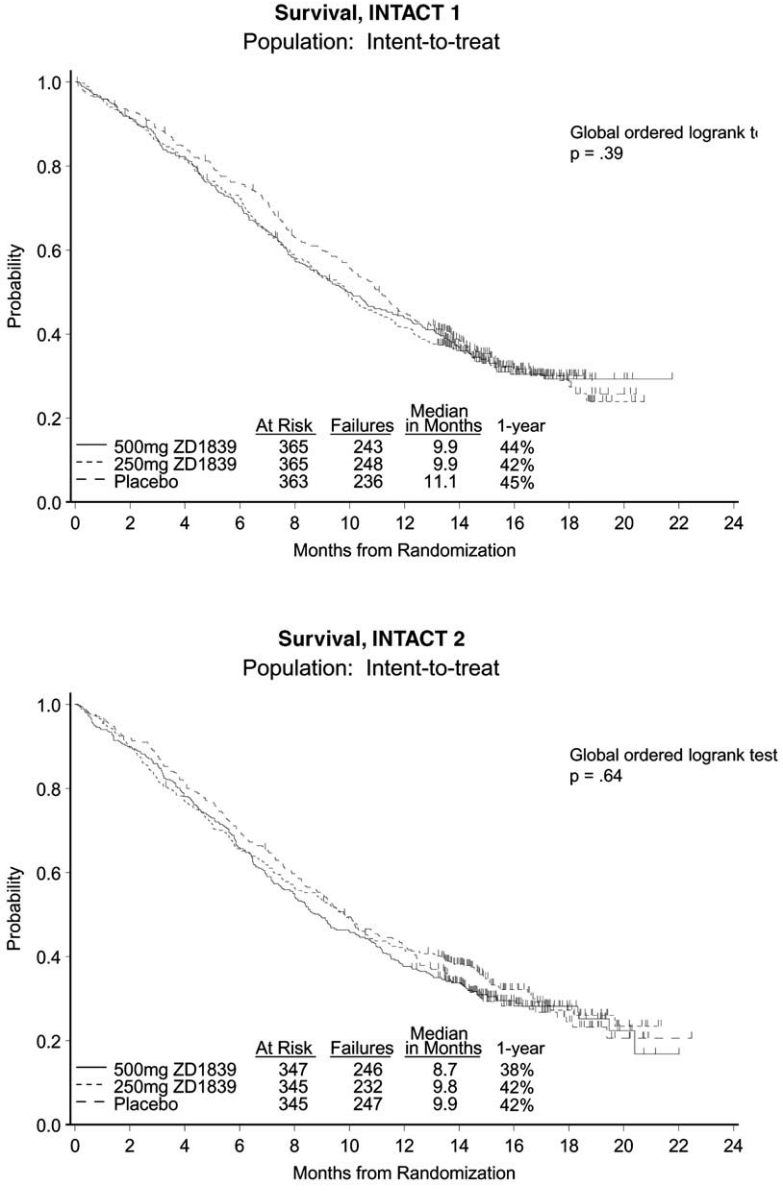


Fig. 4. Gefitinib (Iressa, ZD 1839): NSCLC trial assessing combination treatment [12,13].

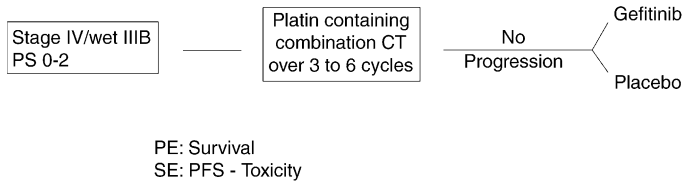


Fig. 5. EORTC 08021: Platin-based-combination chemotherapy followed by adjuvant Gefitinib (Iressa, ZD 1839) in advanced NSCLC.

There was a trent towards improved survival in patients with adeno-carcinoma who had received chemotherapy for 90 days or more in the Gefitinib 250 mg/day arm while this observation was restricted to INTACT 2 results. Furthermore, the multivariat analysis of INTACT data did not show any consistent and demonstrable effects of Gefitinib combined with chemotherapy on known prognostic factors for survival outcome, and did not reveal any new prognostic factors in advanced NSCLC. The toxicity profile of Gefitinib combined with chemotherapy was comparable to chemotherapy alone, with exception of additive, dose dependent diarrhea and skin-rash. Pulmonary toxicity such as dyspnea or cough was reported in 20–24% of the patients in all three treatment arms (IRESSA 500 mg; IRESSA 250 mg; placebo). Pneumonia was diagnosed in about 7% of the patients analyzed with no difference for IRESSA 500 mg, IRESSA 250 mg and placebo. Interstitial lung disease appeared in about 1% with no difference in the three treatment arms. This ILD rate documented in the INTACT trials ranges far below the reported incidence from several Japanese investigators experienced after Gefitinib's registration in Japan and its general availability [16–21].

From the INTACT data presented it can therefore be concluded that Gefitinib in combination with platinum-based doublet chemotherapy for advanced NSCLC does not improve survival. These results are not unique. Other novel combinations with 'gold standard' chemotherapy regimens have also failed to show additive survival benefits.

## 5. Future projects

As NSCLC is a heterogeneous disease, it seems likely that additional clinical benefit will be derived from using Gefitinib in combination with other anticancer agents, either the traditional cytotoxic agents, or newer biologic agents such as angionesis-inhibitors. Trials are underway or planned to investigate and clarify the activity and toxicity of Gefitinib as second-line therapy [22,23]. A number of further trials are ongoing ore planned to determined the benefits of single-agent Gefitinib in different clinical settings as (1) first-line evaluation in unselected chemotherapy-naive patients with advanced disease, (2) maintenance therapy following standard doublet chemotherapy in advanced disease (Intergroup/EORTC 08021) (Fig. 5), (3) first-line single-agent therapy for patients with advanced disease having a performance-status of 2 or 3 or being unable to tolerate chemotherapy (Canadian/UK/Australian-Trial), (4) maintenance-therapy following chemo-radiotherapy and consolidation-Docetaxel in patients with inoperable stage III NSCLC (SWOG 0023), (5) as adjuvant therapy after complete resection of stage IB, II and IIIA NSCLC (Fig. 6) [24], (6) induction single-agent therapy following doublet chemotherapy pre-operatively (EORTC 08013), and (7) as a chemo-preventive agent in former or current smokers with a previous specified smoking-related cancer (SPORE-trial).

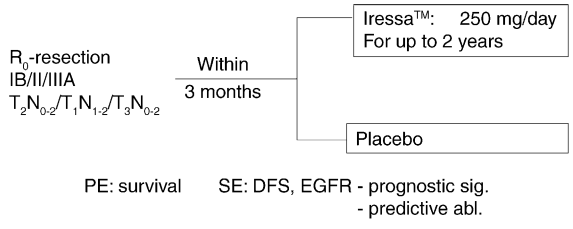


Fig. 6. NCIC CGT BR 19: operable stage NSCLC; phase III—adjuvant Iressa versus placebo.

## 6. Summary

Biologically targeted agents, such as those that selectively inhibit the EGFR, have the potential to provide antitumor activity while being better tolerated than conventional cytotoxic agents. Phase I and II clinical studies demonstrated that Gefinitib single agent therapy is well tolerated and provides clinically significant antitumor activities in patients with advanced NSCLC who have previously received prior treatment with cytotoxic chemotherapy. Large-scale studies to assess the clinical benefit of Gefitinib versus placebo when combined with Cisplatin/Gemcitabine and Carboplatin/Paclitaxel as first-line treatment, however, did not prove that the three drug combinations be able to improve survival when compared to "standard"-doubled chemotherapy. Therefore, at this time, it can be summarized that Gefinitib may provide evaluable addition to the therapeutic options available for the treatment of advanced NSCLC and may also have the potential for its use in early NSCLC.

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