

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**THE USE OF ERLOTINIB IN THE  
MANAGEMENT OF NON-SMALL CELL LUNG  
CANCER**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**March 2006**



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## ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

| <b>Subject</b>  | <b>Date issued</b>     |
|---|------------------------|
| Alglucerase for Gaucher's disease   | July 1997              |
| Taxanes in breast cancer  | July 1997              |
| Somatropin for GHD in adults  | January 1998           |
| New drugs for Alzheimer's disease   | February 1998          |
| Atypical antipsychotics   | February 1998          |
| Dornase alfa for cystic fibrosis  | July 1998              |
| Topotecan for ovarian cancer  | July 1998              |
| Irinotecan for colorectal cancer  | July 1998              |
| Interferon alfa for haematological malignancy   | July 1998              |
| Antiretroviral therapy  | July 1998              |
| Paclitaxel in ovarian cancer  | December 1998 (update) |
| Interferon in MS  | May 1999 (update)      |
| Octreotide  | July 1999              |
| Drug treatment of obesity   | July 1999              |
| Low molecular weight heparins in venous thrombo-embolic disease   | November 1999          |
| Low molecular weight heparins in unstable coronary artery disease   | November 1999          |
| Ribavirin and interferon alfa for chronic hepatitis C   | March 2000             |
| Temozolomide for high grade gliomas   | May 2000               |
| New drugs for rheumatoid arthritis  | May 2000               |
| Verteporfin for age related macular degeneration  | November 2000          |
| Iloprost and epoprostenol in the management of pulmonary hypertension   | February 2001          |
| Atypical antipsychotics in the management of dementia   | June 2001              |
| Interferon alfa in the management of malignant melanoma   | November 2001          |
| Imatinib (Glivec <sup>®</sup> , STI-571), in the management of chronic myeloid leukaemia  | November 2001          |
| Agalsidase alfa and beta in the management of Fabry disease   | July 2002              |
| Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency   | July 2002              |
| Erythropoietin in the management of cancer related anaemia  | July 2002              |
| Drotrecogin alfa (activated) in the management of severe sepsis   | December 2002          |
| An update on newer agents for the treatment of pulmonary hypertension   | February 2004          |
| The use of adefovir dipivoxil for the treatment of chronic hepatitis B infection  | May 2004               |
| The use of teriparatide in the management of osteoporosis   | July 2004              |
| The use of ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases | August 2005            |
| The use of pegvisomant in the management of acromegaly  | January 2006           |
| The use of pemetrexed in the management of malignant pleural mesothelioma   | February 2006          |
| The use of bortezomib second-line in the management of multiple myeloma   | March 2006             |
| The adjuvant use of docetaxel or paclitaxel in the management of early stage breast cancer  | March 2006             |
| The use of ibrutinomab in the management of B-cell follicular non-Hodgkin's lymphoma  | March 2006             |
| The use of rituximab in combination with CVP chemotherapy for the management of follicular non-Hodgkin's lymphoma   | March 2006             |

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## SUMMARY

- Erlotinib is an oral epidermal growth factor inhibitor licensed for the management of non-small cell lung cancer. It is licensed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after failure of at least one prior chemotherapy regimen. Erlotinib is an option to consider for patients with refractory disease with the aim of improving quality of life whilst achieving a modest survival benefit.
- In one phase III trial, erlotinib has been shown to improve overall survival by two months when used as second or third line treatment when compared to placebo. This benefit achieved with erlotinib is similar to that obtained with docetaxel in second line chemotherapy. This group of patients would be unlikely to benefit from further cytotoxic therapies. Some sub groups appeared to derive additional benefit from erlotinib, specifically non-smokers, patients with adenocarcinoma and Asians. This same study also demonstrated benefits in improved quality of life scores with reduced symptoms such as cough, dyspnoea and pain.
- When erlotinib was used first line in combination with a regimen of cytotoxic chemotherapy (currently unlicensed use), no advantage in survival, time to progression or objective response rate was demonstrated over standard chemotherapy alone.
- Erlotinib does not exhibit the typical side effects seen with conventional chemotherapy, such as haematological toxicity. The most common adverse effects are rash and diarrhoea.
- Erlotinib is an additional treatment option. Patient numbers are expected to be between 2 and 8 per 100,000 population. The cost per patient is £1,632 (excluding VAT) per month; with an expectation of around four months' treatment, total cost per patient is £6,528.
- Based on these figures, costs would be expected to be between £13,056 and £52,224 per 100,000. Assuming an overall increased survival time of two months compared to placebo and four months treatment, a crude estimate of cost per life year gained would be £39,168 (assuming the maximum dose of 150mg daily is received).

## BACKGROUND

The incidence of lung cancer in the UK is about 65 per 100,000 population. Non-small cell lung cancer (NSCLC) accounts for about 80% of cases, with the majority of patients presenting with advanced or metastatic disease.<sup>1</sup>

Survival rates for lung cancer are very poor. In England, for patients diagnosed between 1993 and 1995 and followed up to 2000, 21.4% of men and 21.8% of women with lung cancer were alive one year after diagnosis, and only 5.5% of both men and women were alive after five years.<sup>2</sup>

Patients with lung cancer are often more complex and challenging than those with breast or colon cancer, because they frequently have significant additional co-morbidities that can complicate chemotherapy. Adjuvant chemotherapy in NSCLC has been associated with an absolute five-year improvement in overall survival of only 4.1%<sup>3</sup> although recent reports show improvements of up to 14%.<sup>4</sup>

In advanced NSCLC, chemotherapy offers symptomatic relief and a modest improvement in survival. Median time to progression after chemotherapy is three to five months. Docetaxel and pemetrexed are the only agents known to prolong survival among patients with disease progression after first line chemotherapy for NSCLC.<sup>5,6</sup> Few options are available for the treatment of patients with disease progression or those not eligible for second line chemotherapy.<sup>5</sup>

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor regulator type 1 (EGFR/HER1) tyrosine kinase inhibitor. It is a potent inhibitor of the intracellular phosphorylation of EGFR, which is expressed on the cell surfaces of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.<sup>7</sup> EGFR/HER1 is implicated in essential biological processes of malignancy, and is expressed in the majority of NSCLC, but a correlation between expression of EGFR and response (to EGFR inhibitors) has not been identified.<sup>8</sup>

Erlotinib is licensed for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.<sup>7</sup> In September 2005 it was approved in the European Union for the treatment of patients with NSCLC who failed chemotherapy. The company based its application on trial evidence of a median increase in survival of two months in patients with locally advanced or metastatic forms of the disease and improved control of coughing and shortness of breath.<sup>9</sup>

## CURRENT GUIDELINES

The National Institute of Health and Clinical Excellence (NICE) is currently evaluating the erlotinib in the treatment of NSCLC; guidance is expected in December 2006<sup>10</sup>. NICE guidance on the diagnosis and treatment of lung cancer was published in February 2005, and includes the following advice:<sup>2</sup>

Chemotherapy should be offered to patients at disease stages III or IV (Appendix 1, table 1) who have a good performance status (WHO 0, 1 or Karnofsky score of 80-100; Appendix 1, table 2).

Chemotherapy should be a combination of:

- Single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin)
- Single-agent chemotherapy with a third-generation drug can be offered to those who cannot tolerate a platinum combination
- Docetaxel monotherapy should be considered if second-line treatment is appropriate with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy

## EFFICACY

Efficacy of erlotinib has been evaluated in two phase III trials detailed below.

One phase III, randomised, placebo-controlled, double-blind trial (n=731)<sup>5</sup> examined erlotinib in previously treated patients with stage IIIB or IV NSCLC. Patients who had received one or two prior chemotherapy regimens, and were considered not to be eligible for further conventional chemotherapy, were randomly assigned in a 2:1 ratio to receive oral erlotinib 150mg once daily, or placebo.

The primary endpoint was overall survival. Secondary endpoints included progression-free survival, overall response rate, including complete and partial response, duration of response, toxic effects and quality of life.

Seven hundred and thirty one patients underwent randomisation, but 22 were ineligible. All 731 patients were included in the efficacy analyses, and 727 treated patients were included in the safety analyses. 33% of patients had an average Eastern Cooperative Oncology Group performance status of 2 or 3.

Median overall survival in the erlotinib group was 6.7 months compared with 4.7 months in the placebo group (adjusted hazard ratio (HR) 0.70; 95% confidence interval (CI), 0.58-0.85; p<0.001).

The two months improvement in overall survival was similar to that achieved with docetaxel in second line chemotherapy, even though half the patients in this trial were treated after receiving two or more chemotherapy regimens.<sup>5</sup> These patients would be unlikely to benefit from further cytotoxic therapies.<sup>11</sup> 31% of patients were alive at one year, compared to 22% in the placebo group (p<0.001).

Median progression-free survival was 2.2 months in the erlotinib group vs 1.8 months in the placebo group (adjusted HR 0.61; 95% CI, 0.51-0.74; p<0.001). Overall response rate was 8.9%, the rates of complete and partial responses were 0.7% and 8.2% respectively (median duration 7.9 months) for the erlotinib group, and the partial response rate was <1% for the placebo group (p<0.001). Responses were assessed with the use of the Response Evaluation Criteria in Solid Tumours.<sup>12</sup> These responses were not externally validated.

The median times to progression with regards to various quality of life outcomes were:

| Quality of Life Indicator | Placebo    | Erlotinib  | Improvement with Erlotinib | Adjusted p Value |
|---------------------------|------------|------------|----------------------------|------------------|
| Cough                     | 3.7 months | 4.9 months | 1.2 months                 | p=0.04           |
| Dyspnoea                  | 2.9 months | 4.7 months | 1.8 months                 | p=0.03           |
| Pain                      | 1.9 months | 2.8 months | 0.9 months                 | p=0.04           |

Exploratory forward stepwise regression analyses were performed to adjust for treatment effect and to identify prognostic factors for progression free survival and overall survival. Candidate covariates included EGFR expression, sex, age, race or ethnic group, prior radiotherapy, histologic subtype of cancer and smoking status. In this trial, the 8.9% overall response rate was similar to other rates for erlotinib and gefitinib. Response to erlotinib was higher among Asians (p=0.02), women (p=0.006), adenocarcinoma patients (p<0.001), non-smokers (p<0.001) and patients in whom 10% or more of the tumour cells expressed EGFR (p=0.10). It is important to note that this subgroup analysis was not powered to show a benefit. Further analysis showed that Asian origin, adenocarcinoma and a history of not smoking were predictors of survival. Only the interaction between smoking and treatment was significantly predictive of a differential effect on survival.

### **Unlicensed Use**

A second phase III, multicentre, randomised, placebo-controlled trial (n=1079)<sup>13</sup> assigned patients with a good Eastern Cooperative Oncology Group performance status 0 or 1 and previously untreated advanced (stage IIIB or IV) NSCLC to erlotinib 150mg daily or placebo, combined with up to six cycles of carboplatin and paclitaxel, followed by maintenance therapy with erlotinib or placebo.

The primary end point was overall survival. Secondary endpoints included time to progression and objective response rate.

No significant difference in median overall survival was observed (10.6 months in the erlotinib arm vs 10.5 months in the placebo arm [HR 0.995; 95%CI, 0.86-1.16 p=0.95]). Time to progression was 5.1 months for erlotinib and 4.9 months for placebo (p=0.36). The objective response rates of the erlotinib and placebo groups were similar (21.5% vs 19.3%, respectively, p=0.36).

Differences in overall survival were seen in patients dependent on smoking history. For patients who had never smoked; a prolongation in overall survival was seen with erlotinib treatment of 22.5 months versus 10.1 months in the placebo arm (HR 0.49; 95% CI 0.28 – 0.85). In current smokers, median overall survival was 8.4 months with erlotinib vs 9.1 months with placebo, and in previous smokers, was 10.0 months vs 10.9 months respectively.

There was no correlation between the EGFR expression level and clinical outcome. The median duration of treatment on study drug was 4.6 months with erlotinib and 5.3 months with placebo. The mean total dose of erlotinib was 24g.

This trial showed that when erlotinib was combined with cytotoxic chemotherapy, there was no advantage over standard chemotherapy alone.

A single-arm, open label, multicentre, phase II study<sup>14</sup> planned to estimate the objective tumour response rate of erlotinib administered as a single agent to patients with advanced or recurrent metastatic HER1/EGFR-positive NSCLC, who were previously treated with platinum-based combination chemotherapy. Eighty four patients were screened, and 57 enrolled. Patients received erlotinib 150mg/day as a single agent. The primary efficacy variable was the overall response rate, defined as the percentage of patients with complete or partial responses. Secondary objectives were to estimate the stable disease rate, duration of response, time to progression, overall and one-year survival, quality of life outcomes and safety of erlotinib.

The overall response rate was 12.3% (95%CI, 5.1%-23.7%), and the median duration of response was 19.7 weeks (range, 11.7 to 80.3 weeks). The median overall survival time was 8.4 months (95% CI, 4.8-13.9 months) and the one-year survival rate was 40% (95% CI, 28%-54%). Median progression free survival was nine weeks.

The improvements in the incidence of various quality of life indicators are shown below:

| Overall incidence of | Baseline | After erlotinib Therapy | Improvement with erlotinib |
|----------------------|----------|-------------------------|----------------------------|
| Fatigue              | 67%      | 49%                     | 18%                        |
| Dsypnoea             | 61%      | 37%                     | 24%                        |
| Cough                | 60%      | 39%                     | 21%                        |

Although this trial showed a response rate of 12.3%, and improvements in some quality of life indicators, it is unknown whether treatment with erlotinib prolonged survival.

## ADVERSE EFFECTS

Erlotinib does not exhibit the characteristic side effects of conventional chemotherapy such as haematological toxicity. An increased incidence of rash and diarrhoea was seen in erlotinib-treated patients compared to patients on placebo; an adverse effect that is known to be associated with EGFR tyrosine kinase inhibitors. Other adverse effects were similar in incidence and severity when comparing erlotinib to placebo.<sup>13</sup> A summary of some of the more common adverse effects reported in published clinical trials is shown on the next page:

| Adverse Effect                               | Shepherd F A et al 2005 <sup>5</sup> | Herbst R S et al 2005 <sup>13</sup> | Perez-Solar R et al 2004 <sup>14</sup> |
|--|--------------------------------------|-------------------------------------|--|
| Fatigue                                      | 79%                                  | 53.6%                               | 28%                                    |
| Rash   | 76%                                  | 61.7%                               | 67%                                    |
| Anorexia                                     | 69%                                  | Not stated                          | Not stated                             |
| Diarrhoea                                    | 55%                                  | 67.9%                               | 56%                                    |
| Nausea                                       | 40%                                  | 61.2%                               | 25%                                    |
| Vomiting                                     | 25%                                  | 35.4%                               | 19%                                    |
|  |                                      |                                     |  |
| Dose Reductions (due to adverse effect)      | 19%                                  | Not stated                          | 4%                                     |
| Dose Discontinuation (due to adverse effect) | 5%                                   | Not stated                          | 9%                                     |

### Serious adverse effects

In Shepherd et al,<sup>5</sup> toxic effects at grades 3 to 5 were reported. In the erlotinib group vs placebo, rash incidences were 9% vs 0% ( $p < 0.001$ ), diarrhoea 6% vs <1%, respectively ( $p < 0.001$ ), and infection was 2% vs 5%, respectively ( $p = 0.03$ ). 19% of the erlotinib patients required dose reductions because of drug related toxic effects vs 2% of the placebo group, most frequently due to rash (12%) and diarrhoea (5%).

The erlotinib arm of Herbst et al,<sup>13</sup> had a higher incidence of serious adverse effects than the placebo arm (8.6% erlotinib; 2.4% placebo). The most common of these serious events were diarrhoea (3.8% erlotinib vs 1.1% placebo) and rash (0.8% erlotinib vs 0% placebo).

There were five interstitial lung disease like events in the erlotinib arm (1%) and one such event in the placebo arm (0.2%). All were fatal. 61.2% (322) patients in the erlotinib arm and 63.8% (340) in the placebo arm died before the data cut-off. The majority of these were attributed to disease progression. 10.2% (33) of patients died in the erlotinib arm due to an adverse effect, compared to 4.4% (15) in the placebo arm. The majority of the difference was due to infection (7 erlotinib, 1 placebo) and GI events (4 erlotinib, 1 placebo).<sup>13</sup>

In Perez-Soler et al,<sup>14</sup> 17 patients (30%) had at least one grade 3 drug-related adverse event. Dysphagia, pruritis, fatigue, dyspnoea, decreased appetite and anxiety were the only grade 3 drug-related events reported in two patients (the remainder of grade 3 events were reported in one patient only or were not reported), and none was reported in more than two patients. Interstitial pneumonia and grade 4 events were not reported.

Liver function tests must be monitored, especially in patients with co-existent hepatic impairment. Full blood counts should also be carried out. No specific information is provided however with regards to when and how often this monitoring should take place. Signs and symptoms of toxicity, e.g. acneiform rash, headache, persistent diarrhoea, fever and infection, should also be monitored. If new or progressive pulmonary symptoms develop, therapy should be interrupted pending diagnosis. If interstitial lung disease is diagnosed, erlotinib should be discontinued.<sup>15</sup>

## DOSAGE, ADMINISTRATION AND COST

The recommended dose is 150mg orally, administered at least one hour before or two hours after ingestion of food. If dose adjustment is necessary, erlotinib should be reduced in 50-mg steps.<sup>7</sup>

Erlotinib tablets are available in strengths of 100mg and 150mg tablets.<sup>7</sup> The cost of a 30-day supply of erlotinib 150mg daily is **£1,632** (exclusive of VAT) per patient.<sup>7, 16</sup>

The precise duration of treatment within the published clinical trials is not explicit, but based on a median number of four months treatment, and verification from the company of a mean length of treatment of 125 days (from the Shepherd et al trial<sup>5</sup>), the total cost per patient is of the order of **£6,528**. If the median progression free survival of 2.2 months is used as length of treatment, this total cost becomes **£3,590**.

Assuming an overall increased survival time of two months compared to placebo, as seen in the Shepherd et al trial,<sup>5</sup> a crude estimate of cost per life year gained (LYG) would be **£39,168** (assuming the maximum dose of 150mg daily is received for four months treatment).

An estimated incidence of patients likely to be prescribed erlotinib is 2 – 8 per 100,000 per year.<sup>1</sup> Based on these figures, costs would be expected to be between £13,056 and £52,224 per 100,000 (for four months treatment).

## PLACE IN TREATMENT

There is a need for new therapies to treat patients with non-small-cell lung cancer, particularly those with advanced disease who have a poor prognosis after failure of platinum-based chemotherapy. The majority of these patients will not benefit from additional chemotherapy, including taxane regimens.

Erlotinib has demonstrated modest benefits in prolonging overall survival with an absolute benefit of 2 months. This benefit would appear to outweigh the risks of adverse effects, the most common of which are rash and diarrhoea. The benefits of treatment are obtained at the expense of an apparent crude estimate of cost per life year gained of £39,168. If the drug is to be used, some evidence shows that there appears to be an improved response in non-smokers.

## ARRANGEMENTS FOR PRESCRIBING

Treatment should be prescribed and response supervised by an oncologist experienced in the use of anti-cancer therapies. Shared care is not an appropriate option for erlotinib at this time.

## FUTURE DEVELOPMENTS

Clinical trials are currently underway evaluating erlotinib as a first-line therapy, in patients who are chemotherapy-naïve, with a performance status of 2, or who are unfit for platinum-based chemotherapy. Erlotinib is also being tested in combination with bevacizumab.<sup>8</sup>

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## APPENDIX 1: STAGING CLASSIFICATION AND PERFORMANCE STATUS SCALES<sup>2</sup>

There are two systems for staging lung cancer – one for NSCLC (Table 1) and one for SCLC. There are a number of scales that report performance status, WHO and Karnofsky are compared in Table 2.

**Table 1: The TNM staging classification system for NSCLC**

| Primary tumour (T) |  |
|--------------------|--|
| TX                 | Primary tumour cannot be assessed, or tumour proven by presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy   |
| T0                 | No evidence of primary tumour  |
| TIS                | Carcinoma in situ  |
| T1                 | Tumour < 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (that is, not in the main bronchus)   |
| T2                 | Tumour with any of the following features of size or extent: <ul style="list-style-type: none"> <li>– &gt; 3 cm in greatest dimension</li> <li>– involves main bronchus <ul style="list-style-type: none"> <li>– &gt; 2 cm distal to the carina</li> </ul> </li> <li>– invades the visceral pleura</li> </ul> Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| T3                 | Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung   |
| T4                 | Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina, or tumour with malignant pleural effusion or pericardial effusion or with satellite tumour nodules within the ipsilateral primary-tumour lobe of the lung  |

**Table 2<sup>2</sup>: Performance status scales**

| WHO (Zubrod) scale |   | Karnofsky scale |                                   |
|--------------------|---|-----------------|-----------------------------------|
| 0                  | Asymptomatic  | 100             | Asymptomatic                      |
| 1                  | Symptomatic, but ambulatory<br>(able to carry out light work)                         | 90              | Normal activity, minor symptoms   |
|                    |   | 80              | Normal activity, some symptoms    |
| 2                  | In bed < 50% of day (unable to work but<br>able to live at home with some assistance) | 70              | Unable to work, cares for self    |
|                    |   | 60              | Occasional assistance with needs  |
| 3                  | In bed > 50% of day (unable to care for<br>self)                                      | 50              | Considerable assistance           |
|                    |   | 40              | Disabled, full assistance needed  |
| 4                  | Bedridden   | 30              | Needs some active supportive care |
|                    |   | 20              | Very sick, hospitalisation needed |
|                    |   | 10              | Moribund                          |
|                    |   | 0               | Dead                              |

Reprinted from Detterbeck FC et al., editors (2001) *Diagnosis and treatment of lung cancer: An evidence-based guide for the practicing clinician*. Philadelphia: WB Saunders, p 40, with permission from Elsevier.

## APPENDIX 2: SUMMARY OF TRIALS

Key: CI - confidence interval; C - controlled; DB - double blinded; ECOG - Eastern Cooperative Oncology Group; EGFR - epidermal growth factor receptor; HR - hazard ratio; MC - multicentre; NSCLC - non-small cell lung cancer; O - open; Pbo - placebo controlled; R - randomised; SC - single centre.

| Reference                               | Design                            | Intervention                  | Patient Numbers | Inclusion criteria   | Exclusion Criteria   | Primary Outcome   | Results   | Adverse Effects  |
|---|-----------------------------------|-------------------------------|-----------------|--|--|---|---|--|
| Shepherd F<br>A et al 2005 <sup>5</sup> | R, DB; Pbo,<br>Phase III<br>Trial | Oral erlotinib<br>150mg daily | 488             | Patients aged 18<br>years or older, ECOG<br>status between 0 and<br>3 with pathological<br>evidence of NSCLC.<br>Patients had to have<br>received one or two<br>regimens of<br>combination<br>chemotherapy and<br>not be eligible for<br>further chemotherapy. | Patients with prior<br>breast cancer,<br>melanoma or<br>hypernephroma<br>were ineligible, as<br>were those with<br>other malignant<br>diseases except<br>basal cell skin<br>cancer within the<br>preceding 5 years.<br>Also, symptomatic<br>brain metastases,<br>clinically significant<br>cardiac disease<br>within 1 year,<br>ventricular<br>arrhythmias<br>requiring<br>medication and<br>ophthalmologic or<br>gastrointestinal<br>abnormalities. | Primary end-point<br>was overall<br>survival.<br>Secondary end-<br>points included<br>progression-free<br>survival, overall<br>response rate,<br>duration of<br>response, toxic<br>effects and quality<br>of life.  | Median overall survival in<br>the erlotinib group was<br>6.7 months, and in the<br>placebo group was 4.7<br>months (adjusted HR<br>0.70; 95%CI, 0.58-0.85;<br>P<0.001). | 19% of the erlotinib<br>group needed dose<br>reductions due to drug<br>related toxic effects,<br>compared to 2% of the<br>placebo group. These<br>effects were mainly rash<br>(12%) and diarrhoea<br>(5%) - placebo was 0%<br>for both. 5%<br>discontinued erlotinib<br>due to drug-related toxic<br>effects compared to 2%<br>on placebo. |
|   |                                   | Placebo                       | 243             |  |  | Median progression-free<br>survival was 2.2 months<br>in the erlotinib group and<br>1.8 months in the<br>placebo group (adjusted<br>HR 0.61; 95%CI, 0.51-<br>0.74; p<0.001). The<br>rates of complete and<br>partial responses were<br>0.7% and 8.2%<br>respectively (median<br>duration 7.9 months) for<br>the Erlotinib group, and a<br>partial response of <1%<br>for the placebo group. |   |  |

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| Herbst R S et al 2005 <sup>13</sup> | R, MC, Pbo, Phase III trial | Daily oral erlotinib 150mg concurrently with a maximum of 6 cycles chemotherapy (paclitaxel followed by carboplatin) | 539             | Patients aged older than 18 years old with histologically documented stage IIIB or IV NSCLC and ECOG score of 0 or 1. | Prior systemic chemotherapy for NSCLC, symptomatic or untreated brain metastases, prior exposure to agents directed at the HER axis, unstable systemic disease that would preclude chemotherapy treatment, inadequate renal, haematological or hepatic function. | Primary end-point was overall survival. Secondary endpoints included time to progression, objective response rate and duration of response. | Median survival was 10.6 months in the erlotinib arm versus 10.5 months in the placebo arm (HR 0.995; 95%CI, 0.86-1.16 p=0.95)   | The most common events included diarrhoea (3.8% erlotinib vs 1.1% placebo) and rash (0.8% erlotinib vs 0% placebo). The erlotinib arm had a higher incidence of study drug-related serious adverse effects relative to the placebo arm (8.6% erlotinib vs 2.4% placebo). There were five interstitial lung disease-like events in the erlotinib arm (1.0%) and one event in the placebo arm (0.2%). All were fatal. 10.2% (33) patients died in the erlotinib arm due to an adverse effect, compared to 4.4% (15) in the placebo arm. |
|                                     |                             | Daily oral placebo concurrently with chemotherapy x 6 cycles (paclitaxel followed by carboplatin)                    | 540             |   |  |   | Time to progression was 5.1 months for erlotinib and 4.9 months for placebo (p=0.36). The objective response rates of erlotinib and placebo groups were similar (21.5% vs 19.3%, respectively). There was no correlation between EGFR expression and clinical outcome. |   |

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|--|-----------------------|---|-----------------|---|--------------------|---|---|--|
| Perez-Solar R et al 2004 <sup>14</sup> | MC, O, Phase II study | Daily oral continuous dose of 150mg erlotinib | 57              | Patients aged 18 years or older, documented stage IIIB or IV advanced or recurrent metastatic NSCLC, disease progression or relapse after platinum-based therapy, measurable disease and HER1/EGFR positivity. ECOG status of 0 - 2 and adequate bone marrow, hepatic and renal function. |                    | The primary efficacy variable was the overall response rate. Secondary endpoints were duration of overall response, time to progression and survival. | The objective response rate (complete plus partial response) was 12.3% (95%CI, 5.1%-23.7%). Median duration of response was 19.7 weeks (range, 11.7 to 80.3 weeks). The median overall survival time was 8.4 months (95% CI, 4.8-13.9 months) and 1-year survival rate was 40% (95% CI, 28%-54%). | 5 patients (9%) discontinued erlotinib as a result of an adverse event or withdrawal of consent, and 2 additional patients (4%) required dose reduction. Rash and diarrhoea were the most common adverse effects (67% and 56% respectively). |