Title:
Gefitinib for non-small cell lung cancer

A. Details of appraisal group

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Hill RA  , Research Fellow, Clinical Effectiveness
Walley T  , Professor Pharmacology and Therapeutics

B. Full title of research question

To assess the clinical and cost effectiveness of gefitinib (synonym ZD 1839, trade name Iressa) in its licensed indications*, relative to current standard interventions, for non-small cell lung cancer.

* A licensing application (AstraZeneca) for the use of gefitinib in NSCLC is in progress with EMEA/MCA. This protocol has been developed with reference to the proposed indications summarised in the National Prescribing Centre On the Horizon Rapid Review on gefitinib(1) and information made available by NICE. Any changes in any resultant licensed indications may have implications for the review. Any such deviations from this protocol will be highlighted in the review.

C. Clarification of research question and scope

The systematic review will examine the comparative clinical and cost-effectiveness of gefitinib for non-small cell lung cancer.

The anticipated wording of the UK licence indicates that gefitinib should be used “for patients with locally-advanced or metastatic non-small cell lung cancer (NSCLC) who are refractory to both platinum-containing and docetaxel chemotherapy”. Clinically, the review will attempt to compare the effectiveness of gefitinib with best supportive care (BSC) for this group of patients.
If the evidence allows, the review will attempt to identify the criteria for selecting patients for whom this treatment would be particularly appropriate.

The evaluation of economic evidence will include quality assessment of published cost minimisation, cost effectiveness, cost utility and cost benefit analyses. Economic models included in the industry submissions will be critiqued as appropriate. If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of gefitinib versus best supportive care.
D. Report Methods

Search strategy
The following databases will be searched for relevant published literature for the period from 1995\(^1\) to February 2004.

- CENTRAL (Cochrane Central Register of Controlled Trials)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISRCTN Register of Controlled Trials and ISRCTN Register (http://www.controlled-trials.com)
- National Research Register (http://www.update-software.com/national/)
- The Cochrane Library (http://www.update-software.com/cochrane/)
- metaRegister of Controlled Trials and ISRCTN Register (http://www.controlled-trials.com)
- National Research Register (http://www.update-software.com/national/)
- ISRCTN Register of Controlled Trials and ISRCTN Register (http://www.controlled-trials.com)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- ISI Web of Science- Science Citation Index Expanded

Details of the search strategies used to explore EMBASE and MEDLINE are available in Appendix I.

Research groups identified through searches of the information sources listed below will be contacted for information about ongoing trials:

- Cancer.gov (http://cancer.gov/)
- CenterWatch Clinical Trials Listing Service (http://www.centerwatch.com)
- ClinicalTrials.gov – National Institutes of Health database (http://www.clinicaltrials.gov)
- metaRegister of Controlled Trials and ISRCTN Register (http://www.controlled-trials.com)
- National Research Register (http://www.update-software.com/national/)
- The Cochrane Library (http://www.update-software.com/cochrane/)

Bibliographies of previous reviews, retrieved articles and submissions to the National Institute for Clinical Excellence (NICE) will be searched for further studies.

Handsearching of recent issues of cancer journals that might not yet been indexed in electronic databases covering the period from December 2003 to February 2004 will be conducted. Internet resources (including industry supported WebPages) will be examined for information on clinical trials and cost data.

Individual Patient Data (IPD) will be sought from the drug manufacturer (AstraZeneca Pharmaceuticals) in order to complement any published data identified. This will prove useful if published reports do not contain adequate details of important clinical and economic events or do not include sufficient data to inform time to event rates. From a clinical perspective, IPD relating to all outcomes of response (e.g. complete, partial) and survival (e.g. progression free and overall) would be most valuable. In addition, IPD could provide baseline information (e.g. demographic information and number and type of prior therapies) that can be used to test alternative hypotheses. If appropriate, a model will be developed that extends beyond the end of the data collection period of any published trial. To facilitate this, access to data that allows the projection of means of additional months of survival is required. Comparisons of the likely outcomes of treatment with the likely outcomes of no treatment will be performed and patterns in the dataset will be explored to obtain a realistic range of survival benefit. From a health economics perspective, the focus is to identify where survival gain is most likely and how much it costs to achieve this. Access to IPD relating to resource use (e.g. inpatient stays associated with adverse events, cost of drug wastage) is also necessary in order to estimate true cost-effectiveness ratios.

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\(^1\) 1995 is chosen a start search year in order to ensure that all relevant papers are identified, this date gives us a margin of several years before the introduction of gefitinib.
### Inclusion and exclusion criteria

#### a. Inclusion criteria

<table>
<thead>
<tr>
<th>Study design</th>
<th>Clinical effectiveness:</th>
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<tbody>
<tr>
<td></td>
<td>Primarily: Randomised Controlled Trials (RCTs)</td>
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<td></td>
<td>Secondly: In the absence of RCT data, non-RCTs (such as non-randomised Phase I trials)</td>
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<td>will be reported</td>
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<td></td>
<td><strong>Economic evaluation:</strong></td>
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<td></td>
<td>Full economic evaluations that consider both costs and consequences (cost-effectiveness, cost-utility, cost-minimisation and cost-benefit analyses)</td>
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<table>
<thead>
<tr>
<th>Patient population</th>
<th>Individuals with non-small cell lung cancer who are refractory to platinum-based and docetaxel chemotherapies</th>
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<table>
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<tr>
<th>Interventions</th>
<th>Gefitinib (ZD1839, Iressa™) as monotherapy</th>
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<table>
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<tr>
<th>Comparators</th>
<th>Best supportive care (BSC)</th>
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<tr>
<th>Outcomes</th>
<th><strong>Clinical:</strong></th>
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<tr>
<td></td>
<td>• Overall survival</td>
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<td>• Progression free survival</td>
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<td></td>
<td>• Tumour response rate</td>
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<td></td>
<td>• Radiographic response</td>
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<td></td>
<td>• Disease related symptom improvement rates</td>
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<td></td>
<td>• Disease control rates</td>
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<td></td>
<td>• Adverse events</td>
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<td>• Drug related adverse events</td>
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<td>• Withdrawal due to adverse events</td>
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<td></td>
<td>• Dose limiting toxicity</td>
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<td>• Quality of life</td>
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<td></td>
<td><strong>Economic:</strong></td>
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<tr>
<td></td>
<td>• Incremental cost per life year gained</td>
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<td></td>
<td>• Incremental cost per quality adjusted life year gained</td>
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<td></td>
<td>• Incremental cost per progression-free year gained</td>
</tr>
<tr>
<td></td>
<td>• Incremental cost per quality adjusted progression-free year gained</td>
</tr>
</tbody>
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b. Exclusion criteria

RCTs that:
- provide only unplanned, interim findings
- provide data on only a sub-group of the enrolled patients
- are continuing to recruit patients

Quality assessment strategy
All included studies, resulting from our searching, will be assessed for methodological quality. The quality of clinical effectiveness studies will be assessed using criteria based on CRD Report No. 4.(2) Cost effectiveness studies will be quality assessed using criteria updated from the checklist developed by Drummond.(3)

Two reviewers will independently evaluate the quality of the included studies and discuss disagreements where necessary. A third reviewer will be consulted, if necessary, to achieve consensus.

Data extraction strategy
Data from sources located in our search will be extracted as detailed below and will include information listed in Appendix II.

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms. Time permitting, authors (and sponsors) of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed.

Methods of analysis/synthesis

a. Methods of analysis for clinical studies
Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

For binary outcomes, where sufficient data are available, relative treatment effects will be presented in the form of relative risks (RR). For continuous outcomes, mean differences will be calculated. For time to event outcomes, hazard ratios (HR) will be presented. Data will be pooled only if this makes sense clinically and statistically. If estimates of log HR and its variance are not quoted directly in trial reports and IPD are unavailable, alternative aggregate data (e.g., log rank test p-value) will be extracted in order to calculate pooled HR estimates.(4) Heterogeneity between studies will be assessed by considering differences in the (a) study population, (b) intervention, (c) outcome measures and (d) study quality.

b. Methods of analysis for economic studies
Individual study data and quality assessment will be summarised in structured tables and as a narrative description. All potential effects of study quality will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the industry submissions, will be collated and presented as appropriate.
Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

a. Cost data
The primary perspective for the analysis of cost information will be the NHS and personal social services (PSS). Cost data will therefore focus on the marginal direct health service costs associated with drugs and interventions.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases). All cost data will be converted to a single year (2003) in pounds sterling.

Where appropriate costs will be discounted at 3.5% per annum the rate recommended in the current NICE guidance to manufacturers and sponsors of submissions.

b. Assessment of benefits
A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. We anticipate that the main measures of benefit will be improved survival (progression-free and overall) and quality of life.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5%, the rate recommended in the current NICE guidance to manufacturers and sponsors of submissions.

c. Modelling
We will undertake a detailed analysis of the industry model(s), which will include an assessment of strengths and weaknesses and a discussion of the implications of different assumptions.

Our ability to construct an economic model will depend on the data available. A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the literature searches.

Ideally, the results would be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with substantial precision, incremental cost effectiveness analysis or cost minimisation analysis will be undertaken.

Should suitable IPD be made available and depending on the character of any IPD supplied, the nature of any variation in resource use and survival may be explored in the modelling exercise.

d. Sensitivity Analysis
If appropriate, sensitivity analysis will be applied to our model in order to assess the robustness of the results to realistic variations in the levels of the underlying data (e.g. acquisition price of drugs). Where the overall results are sensitive to a particular variable, the sensitivity analysis will analyse the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).

The results of the evaluation will be used to estimate comparative cost-utility/effectiveness ratios under different treatment scenarios based upon appropriate subgroups of patients.
E. Handling the company submission(s)

The Liverpool Reviews and Implementation Group intends to use the industry dossier:
- As a source of data, looking for studies that meet the inclusion criteria (RCTs/other effectiveness as well as cost-effectiveness, cost utility studies and cost benefit analysis).
- To undertake an analysis of any industry models, including the strengths and weaknesses and the implications of different assumptions. The detail to which this can be undertaken will depend on the number and size of company dossiers submitted. Clarification of particular aspects of the model may be sought from the drug manufacturer.

Any 'commercial in confidence' or ‘academic in confidence’ data taken from the submission(s) or other sources will be underlined in our report (followed with an indication of the source of the data in parenthesis).

F. Project Management

a. Timetable/milestones:

<table>
<thead>
<tr>
<th>Submission</th>
<th>Date</th>
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<tbody>
<tr>
<td>Draft protocol</td>
<td>06 January 2004</td>
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<tr>
<td>Finalised protocol</td>
<td>27 January 2004</td>
</tr>
<tr>
<td>Progress report</td>
<td>13 May 2004</td>
</tr>
<tr>
<td>Complete, near final draft report to external reviewers and NICE Technical Lead</td>
<td>25 June 2004</td>
</tr>
<tr>
<td>Final assessment report to NICE</td>
<td>02 August 2004</td>
</tr>
</tbody>
</table>

b. Review Advisory Panel

The Group will recruit an Advisory Panel of experts to support the development of the review. Panel members may advise on specific sections of the review: clinical, healthcare policy, health economics, statistics and review methodology.

c. External Referees

The Technology Assessment Report will be subject to external peer review by at least two clinical experts and one methodological expert. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. External expert referees will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All referees are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external referees’ signed copies to NCCHTA. Comments from the referees and the Technical Lead at NICE, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

d. Competing Interests

No competing interests exist for members of the Assessment Group. Any competing interests relating to the external reviewers will be declared in the final report.
G. Appendices

I Details of MEDLINE and EMBASE search strategies

a. MEDLINE/Pre-MEDLINE Search Strategy (1995 - February 2004)

1. (lung$ adj4 (cancer$ or tum?r or malignanc$)).tw.
2. (lung$ adj4 (oncolog$ or carcinoma$ or neoplas$)).tw.
3. exp lung neoplasms/ all subheadings
4. exp Carcinoma, Non-Small-Cell Lung/ all subheadings
5. or/1-4
6. (gefitinib or iressa or zd1839).af.
7. 5 and 6
8. animal.sh.
9. human.sh.
10. 8 not (8 and 9)
11. 7 not 10


1. exp lung-cancer/ all subheadings
2. (lung$ ADJ (cancer$ OR tumor OR tumour OR malignanc$)).tw.
3. (lung$ ADJ (oncolog$ OR carcinoma$ OR neoplas$)).tw.
4. or/1-3
5. (gefitinib OR iressa OR zd1839).af.
6. 4 and 5
7. (limit 6 to human)

Full details of the searching process will be recorded.
II Details of data extraction

Clinical effectiveness data to be extracted will include, but not be limited to:

Study Details
- Study bibliographic data
- Type of report (abstract, full manuscript, interim report)
- Type of study
- Methodological details of study
- Concomitant therapies
- Details of funding

Participants
- Age
- Sex
- Stage of disease
- Co-morbidity
- Number recruited or accrued

Results (data for all outcomes specified will be extracted as available)
- Overall survival
- Progression free survival
- Tumour response rate
- Disease related symptom improvement rates
- Disease control rates
- Adverse events
- Drug related adverse events
- Withdrawal due to adverse events
- Dose limiting toxicity
- Quality of life
Cost effectiveness data extraction will include, but not be limited to:

**Study characteristics**
- Type of evaluation and synthesis
- Intervention
- Study population
- Time period of study

**Cost data and cost data sources**
- Cost items
- Cost data sources
- Country, currency year

**Outcome data and data sources**
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models

**Cost effectiveness**
- Cost effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions
III Details of quality assessment

a. Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4(2)

• Was the method used to assign participants to the treatment groups really random? (Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)

• Was the allocation of treatment concealed? (Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)

• Was the number of participants who were randomised stated?

• Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?

• Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?

• Were the eligibility criteria for study entry specified?

• Were any co-interventions identified that may influence the outcomes for each group?

• Were the outcome assessors blinded to the treatment allocation?

• Were the individuals who were administered the intervention blinded to the treatment allocation?

• Were the participants who received the intervention blinded to the treatment allocation?

• Was the success of the blinding procedure assessed?

• Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?

• Were the reasons for any withdrawals stated?

• Was an intention to treat analysis included?

Items will be graded in terms of \( \checkmark \) yes (item adequately addressed), \( \times \) no (item not adequately addressed), \( \checkmark / \times \) partially (item partially addressed), \( ? \) unclear or not enough information, NA not applicable or NS not stated.

b. Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond.(3)

• Study question

• Selection of alternatives

• Form of evaluation

• Effectiveness data

• Costs

• Benefit measurement and valuation

• Decision modelling

• Discounting

• Allowance for uncertainty

• Presentation and generalisability of results

All items will be graded as either \( \checkmark \) yes (item adequately addressed), \( \times \) no (item not adequately addressed), \( ? \) unclear or not enough information, NA not applicable or NS not stated.
IV. Background

Lung cancer is the biggest cancer killer in the world, and causes more deaths per annum than breast, prostate and bowel cancer added together.(5)

In the UK, the commonest cause of cancer death for both men and women is lung cancer being responsible for almost 25 percent of all cancer mortality. Moreover, unlike other cancers there has been no significant improvement in survival rates in the past 30 years. In 2001 there were 28,689 deaths in UK from lung cancer (17,564 men and 11,125 women).(6) More women now die of lung cancer than breast cancer in the UK.

The prognosis is poor for patients with lung cancer. Median survival for lung cancer is only 4 months after diagnosis and less than 20 percent of patients survive longer than the first year.(7) The age standardised 5-year survival rate for England is 5.5 percent. In the UK, less than 1 in 10 patients with lung cancer can expect to live for 5 years after diagnosis. Compared with other European countries and the USA, survival of patients in the UK is poor; only 6 in every 100 patients in the UK survive, compared to 14 in every 100 patients in other countries.(8)

There are two major types of lung cancer tumour, usually classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 80 percent of cases and tends to grow and spread more slowly than SCLC. Management strategies are dependent on the type of cancer identified and other relevant factors. Cigarette smoking is by far the most important cause of lung cancer, and accounts for over 80 percent of all cases. The Health of the Nation strategy aims to reduce lung cancer deaths by at least 30 percent in men and 15 percent in women under 75 years of age by 2010.(9) The best way to prevent lung cancer is to stop, or never start, smoking.(10)

There is a range of treatment options (including non-curative interventions) for patients with lung cancer and choice of treatment depends on a variety of factors including tumour type, size, location and general health status of the patient. Treatments and combinations of treatment include surgery, chemotherapy, radiotherapy, endocrine therapy and BSC. BSC is essentially palliative although variable in its components; it may include for example radiotherapy and occasionally chemotherapy. Many treatment alternatives and combinations have significant toxicity with limited efficacy. Currently, docetaxel, having shown survival benefits over best supportive care, is the only approved treatment in the European Union for patients whose cancer has not responded to platinum-based chemotherapy.(11)

The technology

Gefitinib (ZD1839, trade name Iressa™) is an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor that blocks the signal pathways involved in cell proliferation.(12) It has the ability to slow and reduce cancer cell proliferation and can be used to treat locally advanced or metastatic non-small cell lung cancer. Gefitinib is a once daily oral medication (250mg tablet) and can be offered to patients only after prior treatment with both platinum-based and docetaxel chemotherapies. Gefitinib is manufactured by AstraZeneca Pharmaceuticals LP.

Gefitinib is currently licensed in Japan and South Korea. The Japanese Ministry of Health, Labour and Welfare approved it in July 2002. The Australian Therapeutic Goods Association and the US Food and Drug Administration (FDA) have also approved it. Gefitinib is currently licensed in the USA for use as “monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies”.(6) Accelerated approval by the FDA was conditional on AstraZeneca agreeing to undertake further clinical studies in order to fully ascertain the drug’s clinical benefit.(13)

The FDA delayed approval because of the recent reports linking gefitinib with deaths from lung disorders in Japanese patients. It was reported in the Japanese press that 173/473 patient deaths from lung disorders, including interstitial pneumonia, were related to gefitinib. After investigation by the Japanese government, the prescription of gefitinib was restricted and this has reduced the number of
reported side effects. AstraZeneca have also submitted marketing applications for gefitinib in 12 other countries. Gefitinib is currently not approved for prescription in the UK.

Side effects linked to gefitinib include: diarrhoea, rash, acne, dry skin, nausea, vomiting, itching, loss of appetite, weakness and weight loss. Gefitinib carries a special packet warning and is as follows: “may cause interstitial lung disease (ILD). ILD is a serious and life-threatening lung disease. The symptoms of ILD are trouble breathing, with or without a cough or fever. ILD may become severe in a very short period of time... may cause liver damage called hepatotoxicity... may cause eye damage called corneal erosions”.(14) Finally, gefitinib is contraindicated in patients with hypersensitivity to gefitinib or to any component of the drug.

**Current practice issues**
Gefitinib is currently under clinical investigation for use in a wide range of cancers. It is anticipated that, in the future, gefitinib might be used to treat prostate, breast, head and neck, gastric and colorectal tumours as well as NSCLC. Whether or not gefitinib will be used as a monotherapy or in combination with other chemotherapies is the focus of current randomised controlled cancer trials. In NSCLC current thinking is that there is no benefit from adding gefitinib to standard, platinum based chemotherapy and it is therefore only approved by governments as a monotherapy.

The nearest rival drug to gefitinib is tarceva (trade name Erlotinib™). Tarceva is manufactured by Genentech/Roche and phase III trial data are expected to be published in the second half of 2004. An evaluation of tarceva will not form part of this appraisal as BSC is the relevant comparator.

**Economics**
In the treatment of advanced non-small cell lung cancer, small gains in outcome often require the use of intensive and costly interventions.(15) In particular, high costs are generated by hospitalisation, particularly in the later stages of the illness. The provision of palliative care accounts for the greatest part of the cost of services for lung cancer. It has been estimated that the average cost of treatment for each patient with lung cancer is £4,730 (1990 prices).(16)
V References