AstraZeneca UK Ltd,
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# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# SINGLE TECHNOLOGY APPRAISAL (STA)

FOR

## Gefitinib for the first line treatment of locally advanced or metastatic non-small lung cancer

# Glossary

| | |
|---|---|
| **AACR** | American Association for Cancer Research |
| **ACD** | Appraisal Consultation Document |
| **ACTION** | Assessment of Costs and ouTcomes of chemotherapy In an Observational setting in patients with advanced NSCLC |
| **AE** | Adverse Event |
| **ALT** | Alanine Transaminase |
| **ANC** | Absolute Neutrophil Count |
| **aNSCLC** | Locally-advanced or metastatic Non-Small Cell Lung Cancer |
| **ARMS** | Amplification-Refractory Mutation System |
| **ASCO** | American Society of Clinical Oncology |
| **ATC** | Anatomic Therapeutic Chemical classification system |
| **AUC** | Area under the curve |
| **BICR** | Blinded Independent Central Review |
| **BNF** | British National Formulary |
| **BSA** | Body Surface Area |
| **BSC** | Best Supportive Care |
| **CCOHTA** | Canadian Coordinating Office for Health Technology Assessment |
| **CEA** | Cost Effectiveness Analyses |
| **CEAC** | Cost-Effectiveness Acceptability Curve |
| **CI** | Confidence Interval |
| **CR** | Complete Response |
| **CrI** | Credible Interval |
| **CT** | Computed Tomography |
| **CTC** | Common Toxicity Criteria |
| **DIC** | Deviance Information Criterion |
| **Doc/carb** | Docetaxel and carboplatin combination |
| **Doc/cis** | Docetaxel and cisplatin combination |
| **ECCO** | European CanCer Organisation |
| **ECOG** | Eastern Cooperative Oncology Group |
| **EFS** | Evaluable for Safety |
| **EFQ** | Evaluable for health-related quality of life |
| **EGFR** | Epidermal Growth Factor Receptor |
| **EGFR-TKI** | Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor |
| **EGFR-TK M+ or EGFR M+** | EGFR mutation positive |
| **EGFR-TK M- or EGFR M-** | EGFR mutation negative |
| **EMEA** | European Medicines Agency |
| **ERG** | Evidence Review Group |
| **ESMO** | European Society for Medical Oncology |
| **FACT-L** | Functional Assessment of Cancer Therapy - Lung |
| **Gem/carbo** | Gemcitabine and carboplatin combination |
| **Gem/cis** | Gemcitabine and cisplatin combination |
| **g-CSF** | Granulocyte Colony-Stimulating Factor |
| **HR** | Hazard Ratio |
| **HRG** | Healthcare Resource Groups |
| **HRQoL** | Health-Related Quality of Life |
| **IC** | Incremental Cost |
| **ICER** | Incremental Cost-Effectiveness Ratio |
| **ILD** | Interstitial Lung Disease |
| **INTEREST** | IRESSA Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere |
| **IPASS** | IRESSA Pan-ASian Study |
| **ISEL** | IRESSA Survival Evaluation in Lung cancer |

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|---|---|
| **ISPOR** | International Society for Pharmacoeconomics and Outcomes Research |
| **ITT** | Intention-To-Treat |
| **KM** | Kaplan-Meier |
| **LCS** | Lung Cancer Symptoms |
| **LYG** | Life-Years Gained |
| **MTC** | Mixed-Treatment Comparison |
| **MTD** | Maximum Tolerated Dose |
| **N or n** | Number of patients in the treatment arm |
| **N/A** | Not Applicable |
| **NCEPOD** | National Confidential Enquiry into Patient Outcome and Death |
| **ND** | No data |
| **NI** | Non-inferiority |
| **NICE** | National Institute for Health and Clinical Excellence |
| **NR** | Not Reported |
| **NS** | Not (statistically) Significant |
| **NSCLC** | Non-Small Cell Lung Cancer |
| **Od or o.d.** | Once daily |
| **OR** | Odds Ratio |
| **ORR** | Objective reponse rate |
| **OS** | Overall survival |
| **Pac/carb** | Paclitaxel and carboplatin combination |
| **Pac/cis** | Paclitaxel and cisplatin combination |
| **Pem/cis** | Pemetrexed and cisplatin combination |
| **PBAC** | Pharmaceutical Benefits Advisory Committee (Australia) |
| **PBB** | Pharmaceutical Benefits Board (Sweden) |
| **PFS** | Progression Free Survival |
| **PP** | Per Protocol |
| **PPRS** | Pharmaceutical Price Regulation Scheme |
| **PR** | Partial Response |
| **PS 0/1** | WHO Performance Status 0 or 1 |
| **PSA** | Probabilistic Sensitivity Analysis |
| **QALY** | Quality-Adjusted Life-Year |
| **RCT** | Randomised Controlled Trial |
| **RECIST** | Response Evaluation Criteria in Solid Tumours |
| **RR** | Relative Risk |
| **SCLC** | Small-cell lung cancer |
| **SD** | Stable Disease |
| **SIGN** | Scottish Intercollegiate Guidelines Network |
| **SmPC** | Summary of Product Characteristics |
| **SPA** | Single Payment Access scheme |
| **STA** | Single Technology Appraisal |
| **TOI** | Trial Outcome Index |
| **TR** | Total Response |
| **TrR** | Treatment Response |
| **VAS** | Visual Analogue Scale |
| **Vin/carb** | Vinorelbine and carboplatin combination |
| **Vin/cis** | Vinorelbine and cisplatin combination |
| **WB** | Weibull |
| **WTP** | Willingness To Pay |

# Contents

Section A

# 1 Description of technology under assessment

**1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.**

IRESSA (gefitinib)

Pharmacotherapeutic group: Protein kinase inhibitors; ATC code: L01XE0

**1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).**

IRESSA received its marketing authorisation on the 24th June 2009 from the European Medicines Agency (EMEA).

**1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.**

IRESSA is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of Epidermal Growth Factor Receptor (EGFR-TK).

**1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.**

Gefitinib is expected to be commercially available to the NHS on the week commencing 14th September in the UK.

**1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.**

| Country: | Date of authorisation: |
|---|---|
| Japan | 05.07.2002 |
| Australia | 28.04.2003 (Label restricted) |
| USA | 05.05.2003 (Label restricted) |
| Singapore | 22.05.2003 |
| Argentina | 30.05.2003 |
| South Korea | 14.06.2003 |
| Taiwan | 27.08.2003 |
| Malaysia | 29.08.2003 |
| Mexico | 12.09.2003 |
| Philippines | 23.09.2003 |
| Nicaragua | 15.12.2003 |
| Canada | 17.12.2003 (Label restricted) |

| Country: | Date of authorisation: |
|---|---|
| Curacao | 18.12.2003 |
| Dominican Republic | 19.12.2003 |
| Hong Kong | 31.12.2003 |
| Israel | 07.01.2004 (Label restricted) |
| Honduras | 08.01.2004 |
| New Zealand | 22.01.2004 |
| Guatemala | 04.02.2004 |
| United Arab Emirates | 17.02.2004 |
| Thailand | 24.02.2004 |
| Indonesia | 05.03.2004 |
| India | 11.03.2004 |
| Peru | 22.03.2004 |
| El Salvador | 28.04.2004 |
| Bahrain | 04.05.2004 |
| Panama | 05.05.2004 |
| Venezuela | 26.07.2004 |
| Chile | 30.07.2004 |
| Serbia and Montenegro | 10.09.2004 |
| Uruguay | 29.09.2004 |
| Qatar | 13.10.2004 |
| Russia | 30.11.2004 |
| China | 06.12.2004 |
| Sri Lanka | 12.02.2007 |
| Switzerland | 01.02.2004 . (Label restricted) |
| EU | 24.06.2009 |

EU member states: Austria, Belgium, Cyrpus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic, Solvenia, The Netherlands, UK. Plus: Norway, Liechtenstein and Iceland.

**1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?**

Submission to Scottish Medicine Consortium is expected in January 2010 with advice to be published on the SMC website in May 2010.

**1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?**

IRESSA is available as a pack of 30 x 250mg film-coated tablets.

**1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.**

The dosing schedule for gefitinib is 250 mg daily until the disease shows signs of progression. In IPASS, the mean treatment duration for EGFR-TK M+ patients treated with gefitinib 250mg once daily was 8.8 months (median 8.3 months) [1].

**1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details**

**of the anticipated unit cost, including the range of possible unit costs.**

The NHS list price for IRESSA is £2167.71. AstraZeneca proposes to make gefitinib available to the NHS through the Single Payment Access (SPA) scheme, which has been approved by the Department of Health for NICE to review, and to charge the NHS a single Fixed Price for each patient treated with gefitinib. This fee will include the entire cost of a course of treatment of gefitinib until disease progression, irrespective of treatment duration and will be reviewed after 3 years in line with the Pharmaceutical Price Regulation Scheme (PPRS).

### 1.10 What is the setting for the use of the technology?

For this Single Technology Appraisal, the treatment setting for gefitinib is the first-line treatment of previously untreated adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

1.11 **For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?**

Gefitinib only has proven efficacy benefits over doublet chemotherapy in NSCLC patients who are harbouring activating EGFR-TK mutations in line with the marketing authorisation. AstraZeneca has been working with the NHS to ensure equitable access to identifying these patients throughout England and Wales through EGFR-TK mutation testing. NHS centres already testing for the activating EGFR-TK mutation include the Royal Marsden NHS Foundation Trust (London), University Hospital of Wales (Cardiff), University Hospitals Brimingham NHS Foundation Trust (Birmingham) and the Christie NHS Foundation Trust (Manchester). A number of other NHS trusts have indicated that they have the capability to test and AstraZeneca understands that many of these will commence testing imminently. Commercial laboratories have also indicated to AstraZeneca that they have the capability to test for the mutation.

No other medications is required to be administered alongside gefitinib unlike chemotherapy which may require pre-medication with corticosteroids and anti-emetics.

# 2 Statement of the decision problem

| | Final scope issued by NICE | Decision problem addressed in the submission |
|---|---|---|

| | Final scope issued by NICE | Decision problem addressed in the submission |
|---|---|---|
| Population | People with previously untreated EGFR-TK mutation positive locally advanced or metastatic NSCLC | People with previously untreated EGFR-TK mutation positive locally advanced or metastatic NSCLC |
| Intervention | Gefitinib | Gefitinib |
| Comparator(s) | Platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine<br>Pemetrexed in combination with platinum based chemotherapy (carboplatin or cisplatin)<br>Best supportive care | • Gemcitabine and carboplatin<br>• Paclitaxel and carboplatin<br>• Vinorelbine and cisplatin<br>• Gemcitabine and cisplatin |
| Outcomes | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• health-related health-related quality of life<br>• adverse effects of treatment | • overall survival<br>• progression-free survival<br>• response rates<br>• health-related health-related quality of life<br>• adverse effects of treatment |
| Economic Analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Costs to the NHS associated with the testing for EGFR-TK mutations should be included in the economic analysis. | The outcome measures listed in the final scope do capture the most important health-related benefits of gefitinib<br><br>Time horizon - a time horizon of 5 years will be adopted for the cost-effectiveness analysis. This is consistent with the poor prognosis of patients diagnosed with aNSCLC, with fewer than 1% surviving beyond 5 years.<br><br>The cost of EGFR-TK mutation testing will be included in the economic analysis. |
| Subgroups to be considered | If evidence allows: performance status, histology, gender, and previous smoking history | If evidence allows: performance status, histology, gender, and previous smoking history |
| Special considerations, including issues related to equity or equality | | |

## *Section B*

# *3* Executive summary

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| **Disease background** | Lung cancer is the leading cause of cancer death worldwide and is responsible for over 33,000 deaths a year in England & Wales. Non-Small Cell Lung Cancer (NSCLC) is the commonest subtype, accounting for 80% of all lung cancer cases. Despite advances in early detection most patients still present with late stage disease. 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 less than 1 % of advanced NSCLC patients were alive after five years **(see section 4.1).** |
| **Treatment pathway** | The majority of patients with lung cancer are diagnosed, or relapse, with incurable disease and receive palliative treatment only. For otherwise fit patients with stage III / IV non-small cell lung cancer (NSCLC), first-line treatment consists of platinum-based combination chemotherapy followed by docetaxel chemotherapy or erlotinib, at disease relapse, as currently recommended in NICE clinical guidelines **(see section 4.1).**<br><br>To help maintain a patient's functionality, a treatment is required that improves disease-related symptoms (such as dyspnoea, fatigue and pain) and reduces the incidence of adverse events compared to chemotherapy. The ability for the patient to be able to perform everyday functions such as bathing and dressing helps preserve their health-related quality of life and dignity. These factors help highlight the need for a technology that delays disease progression, improves symptoms of the disease with improved health-related health-related quality of life and with a reduced incidence of toxic adverse events to the standard of care in the first line setting, doublet chemotherapy **(see section 4.2).** |
| **Approved name**<br><br>**Brand name** | Gefitinib<br><br>IRESSA |
| **Indication and marketing status** | Gefitinib was granted a marketing authorisation for the treatment of NSCLC adult patients who are EGFR-TK mutation positive (EGFR-TK M+) on 24th June 2009. |
| **Formulation, strength and pack size** | Gefitinib 250mg tablets are available in packs of 30 |
| **Mechanism of action** | The activity of EGFR-TK in cancer cells results in the phosphorylation of downstream proteins that promote cell proliferation, invasion, metastasis, and inhibition of apoptosis. Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase and is an effective treatment for patients with tumours with activating mutations of the EGFR-TK tyrosine kinase domain regardless of line of therapy. |
| **Proposed course of treatment** | The dosing schedule for gefitinib is 250 mg daily until the disease shows signs of progression. In IPASS, the mean duration of treatment with gefitinib for EGFR-TK M+ patients was 8.8 months (median 8.3 months). |

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| **Clinical results of IRESSA in first line NSCLC** | The **I**ressa **P**an-**AS**ian **S**tudy (IPASS) is the first time an EGFR-TKI has proven superiority for progression-free survival (PFS) relative to doublet chemotherapy in a head-to-head phase III study in patients with previously untreated advanced NSCLC. The study demonstrated that PFS for gefitinib 250 mg daily is clinically superior to paclitaxel/carboplatin (paclitaxel 200 mg/m$^2$ intravenously over 3 hours on Day 1, immediately followed by carboplatin AUC 5.0 or 6.0 intravenously over 15 to 60 minutes, in 3-weekly cycles for up to 6 cycles). When analysed by EGFR-TK mutation status, EGFR-TK M+ patients had a statistically significantly improved PFS with gefitinib compared with those treated with paclitaxel/carboplatin (HR: 0.48; 95% CI 0.36, 0.64; p < 0.0001). The opposite was seen in EGFR-TK M- patients. An early analysis of overall survival has been performed, but this is based on a relatively small number of events and follow-up for overall survival is ongoing.<br><br>IPASS has demonstrated that EGFR-TK M+ patients have significantly longer progression free survival and that more of these patients have a sustained and clinically relevant improvement in health-related quality of life on gefitinib compared to doublet chemotherapy **(see section 4.4)**. |
| **Safety** | The most common adverse events (AEs) observed in IPASS were rash/acne and diarrhoea with gefitinib and neurotoxicity, nausea, vomiting and haematologic toxicity with doublet chemotherapy. **(see section 6.7)** |
| **Clinical management of NSCLC** | The clinical management of advanced NSCLC remains challenging, but a targeted oral agent that has superior efficacy, a more favourable tolerability profile, and results in better HRQoL than intravenous chemotherapy is an important shift in the treatment paradigm for NSCLC and offers an additional superior option for selected patients. Based on these data, gefitinib is a valid treatment option for previously untreated locally advanced or metastatic NSCLC patients with harbouring activating mutations in the EGFR-TK. **(see section 6.9)** |
| **Patient Access Scheme** | AstraZeneca proposes to make gefitinib available to the NHS through the Single Payment Access (SPA) scheme and to charge the NHS a single Fixed Price for each patient treated with gefitinib. This fee will include the entire cost of a course of treatment of gefitinib until disease progression, irrespective of treatment duration and will be reviewed after 3 years in line with the Pharmaceutical Price Regulation Scheme (PPRS)**. (see section 10.5)** |
| **Source of clinical evidence for economic evaluation** | Gemcitabine plus carboplatin (gem/carb) was considered the primary comparator in the economic evaluation since this is the most frequently used doublet chemotherapy for advanced NSCLC (aNSCLC) in England and Wales. There are no head-to-head trial data to evaluate the clinical benefits of gefitinib versus gem/carb in an EGFR-TK M+ population of patients with aNSCLC. The clinical evidence for the primary comparison was sourced from a mixed treatment comparison conducted by AstraZeneca UK Ltd. (**see section 6.6**). |
| **Results of the economic evaluation** | The incremental cost-effectiveness ratio (ICER) for gefitinib EGFR-TK M+ versus gem/carb EGFR-TK M+ was £20,744/QALY. There was an 83% probability of gefitinib |

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|---|---|
| | EGFR-TK M+ being a cost-effective use of NHS resource in England and Wales compared to gem/carb at a willingness-to-pay threshold of £30K/QALY. **(see sections 7.3.1.1 and 7.3.2.1)** |
| **Place of IRESSA in the treatment of first line NSCLC** | Gefitinib should be considered the standard of care for the 1st line treatment of patients with aNSCLC who test positive for EGFR mutations and are eligible for doublet chemotherapy. |
| **Estimated budget impact** | The net budget implications for the NHS in England and Wales of adopting gefitinib for the 1st line treatment of aNSCLC in patients tested positive for EGFR-TK mutations was estimated to be £[redacted] in 2010/11 increasing to £[redacted]. in 2014/15. **(see section 8.1)** |
| **Conclusion** | Overall, gefitinib provides a valuable alternative to doublet chemotherapy in EGFR-TK M+ patients suffering with advanced NSCLC. Gefitinib provides clinically superior PFS and a more favourable tolerability profile than the current standard of care, doublet chemotherapy. Gefinitib's availability as an oral tablet allows reduction in administration costs and eliminates the risk associated with intravenous administration. The proposed Single Payment Access (SPA) scheme is an innovative way for the NHS to pay for gefitinib through an upfront one-off fixed payment, allowing patients quick access to effective treatment for advanced NSCLC and giving the NHS predictable budget impact. |

# 4 Context

## 4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Lung cancer is the leading cause of cancer death worldwide and is responsible for over 33,000 deaths a year in England & Wales[2]. Non-Small Cell Lung Cancer (NSCLC) is the commonest subtype, accounting for 80% of all lung cancer cases. Despite advances in early detection most patients still present with late stage disease.

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 less than 1% of advanced NSCLC lung cancer patients were alive after five years[3,4].

The majority of patients with lung cancer are diagnosed with, or relapse with incurable disease and receive palliative treatment only. For otherwise fit patients with stage III / IV NSCLC, first-line treatment consists of platinum-based combination chemotherapy followed by docetaxel chemotherapy or erlotinib, as currently recommended in NICE clinical guidelines[3].

## 4.2 What was the rationale for the development of the new technology?

Chemotherapies are generally non-specific in cellular action; they target preferentially rapidly proliferating cells and do not discriminate between malignant and non-malignant cells, resulting in non-specific, multi-organ toxicity. In addition they tend to be administered at the maximum tolerated dose. As a result, in addition to acute, potentially life-threatening side effects, chemotherapy is also associated with serious longer term toxicities, which has a detrimental effect on a patient's health-related quality of life.

In treating patients with NSCLC, doublet chemotherapy is associated with haematological and non-haematological toxicities including neutropenia, febrile neutropenia, anaemia, thrombocytopenia, asthenia, diarrhoea, fever, infection, nausea, neurosensory disorders, pulmonary disorders, stomatitis and vomiting.

To help maintain a patient's functionality, a treatment is required that improves disease-related symptoms (such as dyspnoea, fatigue and pain) and reduces the incidence of adverse events. The ability for the patient to be able to perform everyday functions such as bathing and dressing helps preserve their health-related quality of life and dignity. These factors help highlight the need for a technology that offers superior efficacy to the standard

of care in the first line setting, doublet chemotherapy, and a reduced incidence of toxic adverse events with improved health-related quality of life.

### 4.3 What is the principal mechanism of action of the technology?

The genetic predisposition to NSCLC is still under intensive investigation, however, studies have shown that the epidermal growth factor receptor (EGFR) and member of the erbB protein family, is frequently over-expressed and activated to a phosphorylated state in NSCLC. The activity of EGFR-TK in cancer cells results in the phosphorylation of downstream proteins that promote cell proliferation, invasion, metastasis, and inhibition of apoptosis. It was the EGFR pathway that gefitinib was developed to target..

Gefitinib is a selective EGFR-TKI, also known as HER1 and erb-1 tyrosine kinase inhibitor. Recent studies have found that tumours of NSCLC patients who are positive for mutated EGFR-TK are more sensitive to gefitinib than wild type EGFR-TK NSCLC patients. This finding explains the improved response in those patients with EGFR-TK mutations.

### 4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Doublet chemotherapy has long been established as the standard of care for the first line treatment of advanced NSCLC with improvements in overall survival demonstrated over best supportive care alone (27% reduction in the risk of death). Following the endorsement by NICE in 2005 platinum-based doublet chemotherapy has become established as the standard first-line treatment for advanced NSCLC patients with good performance status in the UK[3]. Combinations of platinum compounds with third generation compounds of gemcitabine, taxanes, vinorelbine or irinotecan have shown comparable efficacy, with differences in toxicity profiles [5-7]. In general, chemotherapy is associated with acute, potentially life threatening side effects (including neutropenia, febrile neutropenia, neutropenic sepsis, renal impairment and cardiac problems), and serious longer term toxicities (including peripheral neuropathy and sensory neuropathy).

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report on the safety of systemic anti-cancer therapy highlights that patients who become unwell following systemic anti-cancer therapy must get appropriate advice and be seen quickly in order to minimise treatment related morbidity and mortality. The report went on to highlight that 43% of patients suffered treatment related grade 3-4 toxicities. The prominent toxicities experienced were neutropenia, neutropenic sepsis, infection, thrombocytopenia and renal impairment [8]. Added to this is the complexity of treatment administration, dose reduction and treatment delays and the provision of procedures for emergency admissions which are all part and parcel of managing the patient being administered chemotherapy.

Gefitinib has demonstrated superior efficacy to paclitaxel and carboplatin doublet chemotherapy in a chemotherapy-naïve EGFR-TK M+ NSCLC population. For these patients, the **I**ressa **P**an-**AS**ian study (IPASS) demonstrated that EGFR-TK M+ patients have significantly longer

progression free survival and that more of these patients have a sustained and clinically relevant improvement in quality of life on gefitinib compared to doublet chemotherapy [9]. Therefore these patients need to be identified by EGFR mutation testing and given gefitinib over platinum-containing doublet chemotherapy.

For the NHS, gefitinib offers reduced stress on overburdened chemotherapy services, reduced numbers of emergency admissions for the treatment of doublet chemotherapy toxicity and reduced costs associated with the management of doublet chemotherapy-associated toxicities.

Gefitinib's oral route of administration makes it easy to administer and eliminates any intravenous-related complications such as phlebitis or extravasation.

### 4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Testing for activating EGFR-TK mutations is not routinely done within the NSCLC treatment pathway in the NHS. There is currently uncertainty around whether there will be regional variation in access to EGFR-TK mutation testing in the UK. It is also currently unknown if clinicians will use clinical characteristics to pre-select NSCLC patients for EGFR-TK mutation testing.

The NICE clinical guidelines recommend for the first line treatment of NSCLC chemotherapy doublet regimen of a platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine. There is uncertainty over what doublet regimen represents best or routine clinical practice within the UK. No national audit has been conducted within the NHS. The ACTION (**A**ssessment of **C**osts and ou**T**comes of chemotherapy **I**n an **O**bservational setting in patients with advanced **N**SCLC) study found that 67.4% of NSCLC patients in the UK received gemcitabine/carboplatin chemotherapy and this has been supported by expert opinion from within the NHS[10].

### 4.6 Provide details of any relevant guidelines or protocols.

In the UK, NICE produced comprehensive guidelines on the management of lung cancer at the beginning of 2005. These guidelines included a recommendation that the current standard of care for the first line treatment of NSCLC is the chemotherapy doublet regimen of a platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine[3].

# 5 Equity and equality

## *5.1 Identification of equity and equalities issues*

**Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?**

Gefitinib enables care to be provided at home, meeting the patient's needs, not just clinically but also in terms of dignity and respect. This is especially the case in rural areas where specialised chemotherapy services are not so easily accessible and also in patients who have mobility needs due to the debilitating nature of NSCLC. A recent National Audit Office report on End of Life Care concluded that reducing the amount of time people approaching the end of their life spend in hospital could make resources available which could be used to better support people in their preferred place of care[11].

There is a strong association between incidence and mortality rates of NSCLC and levels of deprivation. In an analysis of 1993 lung cancer incidence data for England and Wales by Carstairs deprivation index, incidence was almost 2.5 times higher in the most deprived male groups compared to the least deprived –the difference for women was even greater at 3 times[2]. These findings were corroborated by a study in association with the United Kingdom Association of Cancer Registries (UKACR) that found if the incidence of lung cancer was decreased to that of the least deprived group, it would prevent 36% of lung cancer cases in men and 38% of lung cancer cases in women[12].

The use of pre-selection criteria for EGFR-TK mutation testing based on clinical characteristics such as gender, smoking history and histology. There is a risk that NSCLC patients with EGFR M+ tumours who do not have these clinical characteristics will not be identified and therefore denied access to gefitinib.

Equity of access to EGFR-TK mutation testing throughout England and Wales for all NSCLC patients whose EGFR mutation status is unknown.

**How has the analysis addressed these issues?**

The inclusion of AstraZeneca's Single Payment Access scheme ensures that all eligible patients will have unrestricted access to an evidence-based therapy for first-line treatment of NSCLC in EGFR-TK M+ patients regardless of socio-economic status. Gefitinib's oral formulation and well-tolerated adverse event profile should allow patients to reduce the amount of time spent in hospital in keeping with the National Audit Office's findings.

AstraZeneca has adopted a 'test all' strategy to ensure that all NSCLC patients eligible for gefitinib are identified. This patient-centred strategy has been implemented in the Cost Effectiveness analysis (see section 7)

Gefitinib only has proven efficacy benefits over doublet chemotherapy in NSCLC patients with EGFR-TK M+ tumours in line with the marketing authorisation. AstraZeneca has been working with the NHS to ensure equitable access to identifying these patients throughout England and Wales through EGFR-TK mutation testing. NHS centres already testing for the activating EGFR-TK mutation include the Royal Marsden NHS Foundation Trust (London), University Hospital of Wales (Cardiff), University Hospitals Brimingham NHS Foundation Trust (Birmingham) and the Christie NHS Foundation Trust (Manchester). A number of other NHS trusts have indicated that they have the capability to test and AstraZeneca understands that many of these will commence testing imminently. Commercial laboratories have also indicated to AstraZeneca that they have the capability to test for the mutation

# 6 Clinical evidence

## *6.1 Identification of studies*

The strategies for retrieving the relevant clinical data is discussed in further detail in section 6.6.

## *6.2 Study selection*

### 6.2.1 Complete list of RCTs

The search strategy identified 1220 deduplicated references (1012 from Embase, 357 from MEDLINE and 44 from CENTRAL).

### 6.2.2 Inclusion and exclusion criteria

**Inclusion:** First line setting; gefitinib monotherapy, doublet chemotherapy comparator, EGFR-TK mutation subgroup analysis, NSCLC

**Exclusion:** Second and third line setting, gefitinib in combination with chemotherapy

### 6.2.3 List of relevant RCTs

IPASS (**I**ressa **P**an **AS**ian **S**tudy)[9]

IPASS is the phase III head to head comparison of gefitinib to doublet chemotherapy (the current of standard of care in the UK for the treatment of NSCLC in the first-line setting). In this study clinically selected patients with stage IIIB/IV chemo-naïve NSCLC were randomised to receive either gefitinib or doublet chemotherapy (paclitaxel/carboplatin) and was conducted in East Asian countries only. Paclitaxel/carboplatin is one of many doublet

chemotherapy regimens used for the first line treatment of NSCLC and was chosen for this study as it is the predominantly used regimen in East Asian countries.

The selection of patients on the basis of the clinical factors of never-smoking/ex-light smoking status and adenocarcinoma histology, and the geographical location of the study in Asia was based on good efficacy observed in these subgroups in previous studies[13]. It had also been reported that the EGFR-TK mutation rate was higher in patients with these characteristics, and so this selected a population that was enriched for EGFR-TK mutation.

In IPASS, the hazard ratio [HR] for progression-free survival (PFS) for gefitinib versus doublet chemotherapy in the overall study population was 0.74 (95% confidence interval [CI]: 0.65–0.85; $p < 0.0001$). When the pre-planned analysis by EGFR-TK mutation status, EGFR-TK M+ patients had a statistically significantly improved PFS with gefitinib compared with those treated with paclitaxel/carboplatin (HR: 0.48; 95% CI 0.36, 0.64; $p < 0.0001$). For EGFR-TK M- (EGFR-TK M-) patients, on the other hand, chemotherapy provided better PFS (HR: 2.85; 95% CI 2.05, 3.98; $p < 0.0001$). These results established the strong predictive value of EGFR-TK mutation status for the efficacy of targeted treatment with gefitinib.

INTEREST and ISEL were two large phase III randomised studies in pre-treated NSCLC conducted in predominantly Caucasian populations with resulting smaller M+ subgroups. Both studies demonstrated consistent results with IPASS in the M+ subgroups analysed[13,14].(The outcomes of INTEREST in the EGFR-TK M+ sub-group are discussed in more detail in section 6.9.2). ISEL did not meet its primary endpoint of demonstrating superiority of gefitinib over placebo for overall survival in the pre-treated setting, but did demonstrate overall survival benefits in a pre-planned analysis of Asian patients and never smokers, subgroups known to have a higher incidence of EGFR-TK mutations[13].

Two phase III studies have recently reported at the ASCO 2009 and WCLC 2009 comparing gefitinib to doublet chemotherapy regimens for the first line treatment of NSCLC {(Kobayashi et al 2009, Lee et al 2009)}. The outcomes of these studies are described in more detail in sections 6.4 and 6.5.

### 6.2.4 List of relevant non-randomised controlled trials

None identified

### 6.2.5 Ongoing studies

IPASS - ongoing follow up only for overall survival

## *6.3 Summary of methodology of relevant RCTs*

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### 6.3.1 Methods

| STUDY | DATA SOURCE | DESIGN |
|---|---|---|
| **IPASS** | Mok et al 2008 (A)[15]<br>Fukuoka et al 2009 (A)[16]<br>Mok et al 2009 (P) [9] | Randomised, open-label, parallel-group study of gefitinib compared with paclitaxel/carboplatin as first-line treatment in clinically selected patients with advanced NSCLC in East Asia.<br><br>The primary endpoint was progression-free survival. Secondary end-points included overall survival (early analysis; follow-up ongoing), objective response rate, health-related quality of life, disease-related improvements, safety, and tolerability. Evaluation of efficacy by baseline EGFR-TK biomarker status was a planned exploratory objective<br><br>1217 patients were randomised 1:1 to receive gefitinib (250 mg/day orally) or paclitaxel/carboplatin (paclitaxel 200 mg/m2 intravenously over 3 hours on Day 1, immediately followed by carboplatin AUC 5.0 or 6.0 intravenously over 15 to 60 minutes, in 3-weekly cycles for up to 6 cycles).<br><br>Randomisation used dynamic balancing with respect to performance status (0-1, 2), smoking history (never, ex-light ex-smokers), gender, and center. Treatment continued until disease progression, unacceptable toxicity, patient/physician request to discontinue, severe protocol noncompliance, or six chemotherapy cycles were reached. The patients assigned to gefitinib whose tumor progressed were offered carboplatin/ paclitaxel; however, if the patient declined or was considered unsuitable, he/she could receive another approved therapy of the physician's choice. Following progression on paclitaxel/carboplatin, subsequent therapy was at the physician's discretion. |

**Duration of Therapy in IPASS**

Overall exposure to first line study treatment was longer with gefitinib than paclitaxel/carboplatin treatment (medians of 5.6 months and 4.1 months, respectively and means of 6.4 and 3.4 months, respectively). Post-hoc analyses of time on treatment for patients by EGFR-TK mutation status were performed after reviewing the efficacy results by EGFR-TK mutation status (Table 1). Median overall exposure to first-line gefitinib was 8.3 months in EGFR-TK mutation positive (EGFR-TK M+) patients (N=132), 5.9 months in EGFR-TK mutation unknown patients (N=384) and 1.6 months in EGFR-TK mutation negative (EGFR-TK M-) patients (N=91). Median overall exposure to first-line paclitaxel/carboplatin was 4.1 months in all EGFR-TK M+, M-, and unknown subgroups (N=129, 85 and 375, respectively).

**Table 1: Summary Statistics of Total Days on First Line Treatment in EGFR-TK M+ patients**

| | Treatment Received | | |
|---|---|---|---|
| | **Gefitinib** | **Paclitaxel/Carboplatin** | **ALL** |
| | **n = 132** | **n =129** | **n = 261** |
| Mean | 268.1 | 108.2 | 189.1 |
| SD | 156.5 | 36.0 | 139.3 |
| Median | 252 | 126 | 134 |
| **Median (month)** | **8.3** | **4.1** | **4.4** |
| Minimum | 14 | 21 | 14 |
| Maximum | 694 | 160 | 694 |

**Post-discontinuation Treatment following first-line therapy in IPASS**

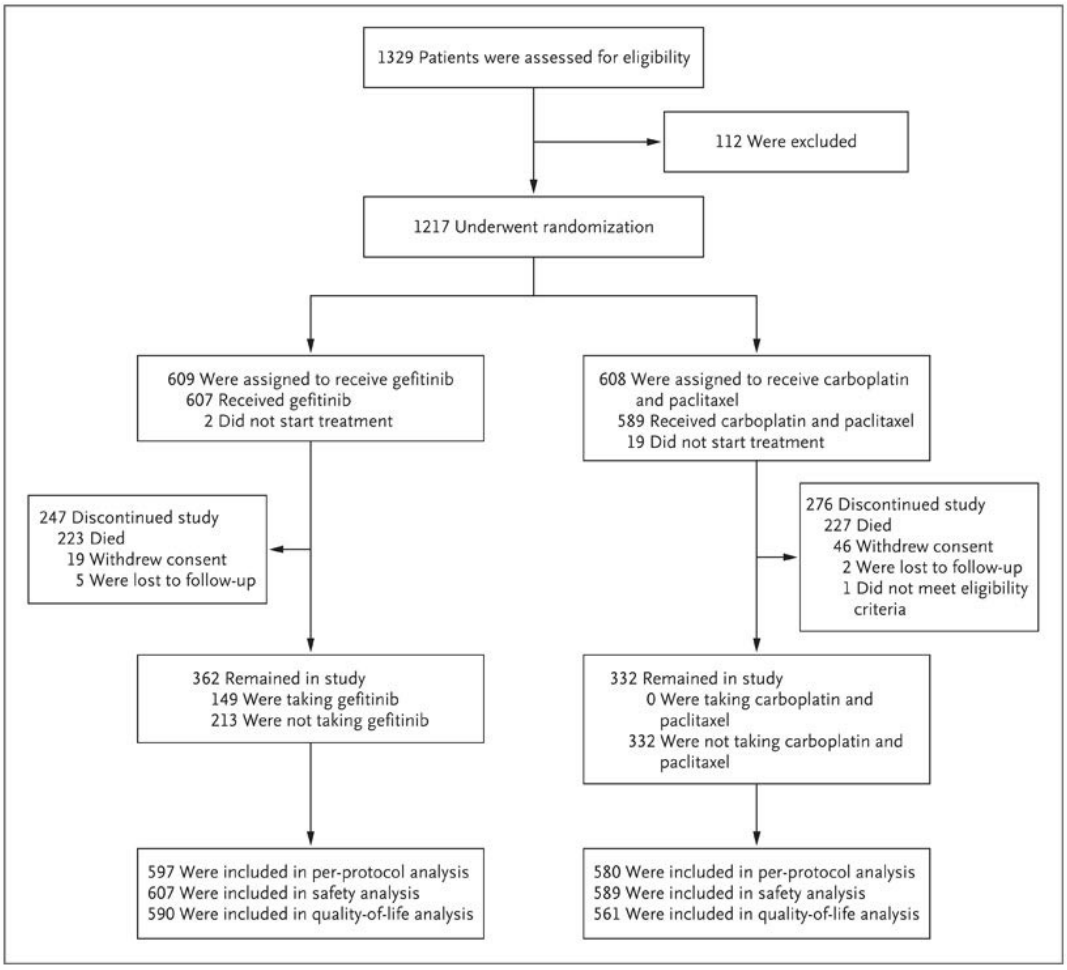
In the EGFR-TK M+ sub-group, 46% of patients in the gefitinib arm received no further treatment apart from further EGFR-TKI therapy (16% received nothing and 28% were still on randomised therapy at the point of analysis). Forty one percent of patients in the gefitinib arm received paclitaxel/carboplatin (39% was second line) and 13% of patients received other chemotherapy following gefitinib. For patients that were on randomised paclitaxel/carboplatin treatment, 39% of patients received no further treatment. Fifty percent of the patients in the doublet chemotherapy arm went on to receive an EGF-TKI at any point (38% gefitinib, 7% erlotinib and 6% other EGFR-TKI) and 11% went on to receive other chemotherapy. These subsequent therapies are likely to confound the interpretation of the overall survival data in this study. However, they should have little effect on all other efficacy endpoints as these are only measured up until progression.

### 6.3.2 Participants

IPASS was conducted in a clinically pre-selected study population which was enriched for clinical characteristics which showed benefit in previous gefitinib studies[13]. Patients were considered EGFR-TK M+ if one of 29 EGFR-TK mutations was detected by Amplification Refractory Mutation System (ARMS) using the DxS EGFR-TK 29 mutation detection kit. Patients were deemed EGFR-TK M- if samples were successfully analysed and none of the 29 EGFR-TK mutations was detected. Eligibility criteria included: age >18 years; histologically or cytologically confirmed stage IIIB or IV NSCLC with **adenocarcinoma histology (including Bronchoalveolar carcinoma); never smokers (<100 cigarettes lifetime) or light ex-smokers (stopped smoking ≥15 years previously and smoked ≤10 pack-years)**; and no prior chemotherapy, biological, or immunological therapy (for full detailed inclusion and exclusion criteria in IPASS see section 10.6, Appendix 6).

Patient baseline characteristics for IPASS study were well balanced between the two groups and are provided in section 10.6, Appendix 6

### 6.3.3 Patient numbers




| Population | Number of patients | Definition |
|---|---|---|
| **Intention to Treat (ITT)** | **1217** | All randomised patients |
| **Per Protocol (PP)** | **1177** | A subset of the ITT population, which includes patients who did not significantly deviate at entry (ie, inclusion/exclusion criteria) or significantly deviate from the protocol |
| **Evaluable for Safety (EFS)** [a] | **1196** | A subset of the ITT population which includes all patients who received at least 1 dose of study medication (gefitinib, or carboplatin or paclitaxel) |
| **Evaluable for Health-related quality of life (EFQ)** | **1151** | A subset of the ITT population containing patients with an evaluable baseline HRQoL assessment and at least 1 evaluable post-baseline HRQoL assessment [b] |

a If no patients were mis-randomised, the EFS population differs from the ITT population in that patients who received no study treatment are excluded
b Patients who answered ≥4 out of the 7 LCS questions at 1 or more of the 3-weekly visits as well as at baseline.

### 6.3.4 Outcomes

The primary endpoint in IPASS was to compare progression-free survival for gefitinib and paclitaxel/carboplatin.

Progression-free survival was assessed from the date of randomisation to disease progression, determined by the Response Evaluation Criteria in Solid Tumors (RECIST), or death from any cause.

Secondary endpoints included overall survival (early analysis; follow-up ongoing), objective response rate, health-related quality of life, symptomatic improvement, safety, and tolerability.

Overall survival was assessed from the date of randomisation to death from any cause. Tumor response was assessed every 6 weeks until disease progression. Health-related quality of life was assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) and Trial Outcome Index ([TOI], sum of the physical and functional well-being, and lung cancer symptoms [LCS] domain scores of FACT-L) scores. Symptoms were assessed by LCS score. The FACT-L questionnaire was collected at randomisation, week 1, then 3-weekly until day 127, then 6-weekly until disease progression, and at discontinuation. Clinically relevant improvement was predefined as $\geq$ 6-point improvement for FACT-L and TOI or $\geq$2-point improvement for LCS maintained for at least 21 days. Safety and tolerability were assessed according to National Cancer Institute Common Terminology Criteria Version 3.0.

Evaluation of efficacy by baseline EGFR-TK biomarker status was a planned exploratory objective.

Tumor samples from consenting patients were analyzed at two central laboratories to determine biomarker status, with EGFR-TK mutation status the first priority. Patients were considered EGFR-TK M+ if one of 29 activating EGFR-TK mutations was detected by Amplification Refractory Mutation System (ARMS) using the DxS EGFR-TK 29 mutation detection kit.

### 6.3.5 Statistical analysis and definition of study groups

Analysis of the primary endpoint (progression-free survival) used a Cox proportional hazards model in the intent-to-treat population (all randomised patients) to assess the non-inferiority of gefitinib compared with paclitaxel/carboplatin with covariates of WHO performance status (0-1, 2), smoking history (never, ex-smoker), and sex. To conclude non-inferiority, the 95% confidence interval (CI) for the hazard ratio (HR) had to lie entirely below the predefined non-inferiority limit of 1.2. A total of 944 progression events were needed for 80% power to conclude non-inferiority if the treatments were truly equal, with a 2-sided 5% probability (significance level) of concluding non-inferiority in error. If the CI for the HR was also below 1, then the P value would be <0.05 and superiority could be concluded from the same analysis without statistical penalty (closed test procedure).

Planned subgroup analyses were conducted comparing progression-free survival between treatments in groups defined by WHO performance status, smoking history, gender, age at randomisation, disease stage at screening, and biomarkers. Treatment-by-covariate interaction tests were used to identify predictive factors by assessing if the progression-free survival treatment effect (HR) was statistically different between subgroups.

Overall survival was analysed using similar methods to progression-free survival. An early analysis is presented; overall survival follow-up is ongoing. Objective response rate (intent-to-treat population), health-related quality of life, and symptom improvement rates (evaluable-for-health-related quality of life population were assessed using a logistic regression model with the same covariates as progression-free survival to calculate odds ratios (ORs, gefitinib: paclitaxel/carboplatin) and 95% CIs. Planned subgroup analyses of objective response rate were conducted as for progression-free survival.

Adverse events were summarised in the evaluable-for-safety population. The incidence rates of 10 specified safety events (five possibly associated with each study treatment) were compared using Fishers exact test, with multiplicity adjustment using the Westfall and Young method.

### 6.3.6 Critical appraisal of relevant RCTs

| Criteria for Critical Appraisal | IPASS |
|---|---|
| How was allocation concealed? | Open-label<br><br>Although the study was open-label, the EGFR-TK mutation status was not known by either the patients or the clinicians during the conduct of the study, and thus would not have affected the efficacy outcomes. It is not practical to blind an intravenous chemotherapy (that requires specialist administration and pre-medication) versus an oral tablet, with both drugs also having very well established and different side-effect profiles. |
| What randomisation technique was used? | Centralised Registration/ Randomisation Center. Randomisation was via a central IVR (Interactive Voice Response) telephone system to receive in a 1:1 ratio gefitinib or paclitaxel/carboplatin. The stratification factors for randomisation were smoking status; performance status; smoking status (non-smoker or ex-light smoker); gender; and centre. |
| Was a justification of the sample size provided? | The sample size goal is to conclude non-inferiority, the 95% confidence interval (CI) for the hazard ratio (HR) had to lie entirely below the predefined non-inferiority limit of 1.2. A total of 944 progression events were needed for 80% power to conclude non-inferiority if the treatments were truly equal, with a 2-sided 5% probability (significance level) of concluding non-inferiority in error. If the CI for the HR was also below 1, then the P value would be <0.05 and superiority could be concluded from the same analysis without statistical penalty (closed test procedure). The analysis also included an evaluation of the efficacy of gefitinib compared to paclitaxel/carboplatin in pre-planned subgroups including the EGFR-TK M+ population. |
| Was follow-up adequate? | Median follow-up (defined as time from randomisation to progression or censoring) for the primary endpoint of progression free survival was 5.6 months. A total of 950 |

| Criteria for Critical Appraisal | IPASS |
|---|---|
| | progression events had occurred at this time (950/1217, 78% maturity), sufficient to meet the target of at least 944 events. At the time of data cut-off, 450 deaths had occurred (450/1217, 37% maturity). An early analysis was performed, however survival follow up will continue and the final analysis of the secondary endpoint of overall survival will take place when at least 944 deaths have occurred. |
| Were the individuals undertaking the outcomes assessment aware of allocation? | Yes - for efficacy and safety variables.<br>No - for determination of EGFR mutation (and other biomarker) status |
| Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely. | Parallel group |
| Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice? | No<br>This study included patients from 87 centers in China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand<br>Clinical practice is similar to that in the UK at the time the study was conducted. The doublet chemotherapy regimen used in the IPASS study is used in the UK along with other combination regimens which have demonstrated similar clinical efficacy to paclitaxel/carboplatin[6,17-19]. |
| How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting. | IPASS was conducted in a clinically pre-selected study population recruited patients who were never or ex-light smokers with adenocarcinoma histology which showed benefit in previous gefitinib studies [13]. From a planned subgroup analysis, IPASS showed that EGFR-TK mutation status was driving the benefit.<br>The patients in the RCT are a good representative sample of patients who are likely to receive doublet chemotherapy in the UK in terms of important prognostic characteristics such as stage of disease and performance status, as outlined in current clinical guidelines considered in UK clinical practice. Therefore the IPASS EGFR-TK M+ population can be considered to be representative of the UK EGFR-TK M+ population. The EGFR-TK mutation is the same in all NSCLC patients regardless of ethnicity and patient characteristics and gefitinib should work the same in all EGFR-TK M+ patients. |
| For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics? | Gefitinib: 250mg once daily<br>Paclitaxel (200mg/m$^2$)/Carboplatin (AUC 5/6) on day 1 every 3 weeks<br>These doses are within the dosage regimens contained in the relevant UK SmPCs |
| Were the study groups comparable? | Yes, demographic and baseline characteristics were well balanced between the two treatment groups and the population was representative of the advanced NSCLC population clinically selected for this study. |
| Were the statistical analyses used appropriate? | Yes, the analyses were pre-specified in the protocol at the start of the study and a comprehensive statistical analysis plan was prepared before database lock and analysis |
| Was an intention-to-treat analysis undertaken? | Yes |
| Were there any confounding factors that may | Evaluation of patient scans in this open-label study did not include a |

| Criteria for Critical Appraisal | IPASS |
|---|---|
| attenuate the interpretation of the results of the RCT(s)? | blinded independent central review (BICR). Although there could be potential for some bias to be introduced in the measurement of PFS and ORR, RECIST criteria were used and tumour responses were calculated programmatically based on tumour measurements for target lesions (as opposed to investigator assessment of tumour response) to increase the robustness of these endpoints.<br>In addition, the clear difference in PFS efficacy results for patients with epidermal growth factor receptor (EGFR) mutation positive status compared with those who are EGFR mutation negative in the IPASS study indicates that the RECIST data are robust because the EGFR mutation status of patients was not known at the time the scans were evaluated.<br>Further, additional analyses that investigated evaluation-time bias (differential assessment frequency between arms) did not indicate any bias in favour of gefitinib.<br>In conclusion, given the level of superiority observed for gefitinib in the IPASS study, progression assessments are considered robust and not affected by bias due to lack of central radiological review in this open label study |

## *6.4 Results of the relevant comparative RCTs*

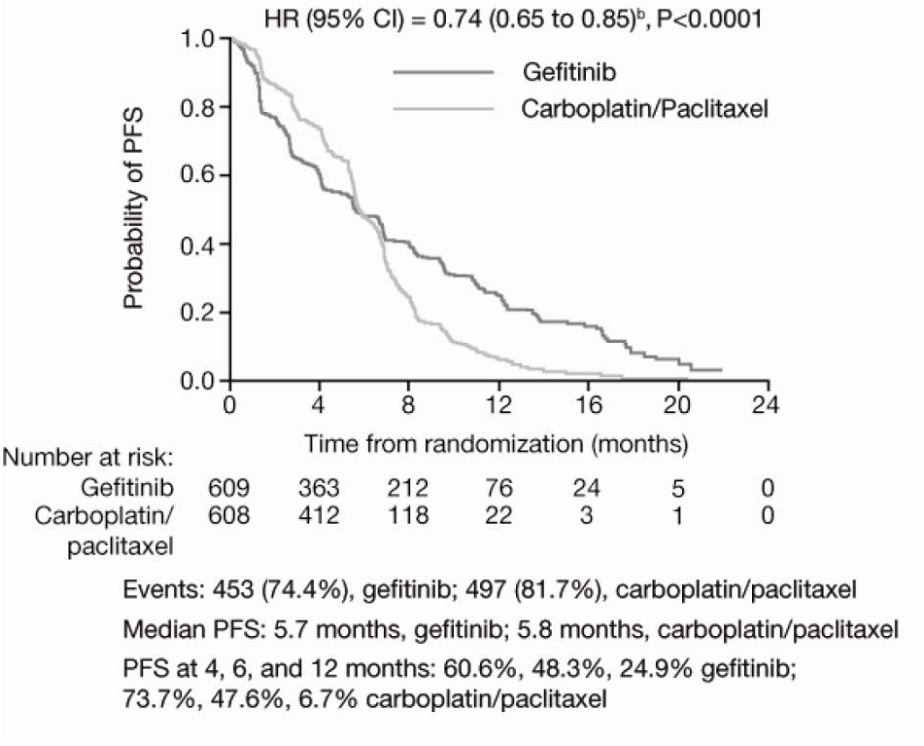
### Primary Endpoint

The primary endpoint of IPASS is progression-free survival.

### PFS in ITT Population

IPASS met its primary objective of demonstrating non-inferiority of gefitinib to doublet chemotherapy. Furthermore, IPASS demonstrated superior progression-free survival to doublet chemotherapy HR 0.74, 95% CI 0.65 to 0.85, P<0.0001. The probability of being progression-free favoured paclitaxel/carboplatin in the first 6 months and gefitinib in the following 16 months (Figure 1). Median progression-free survival was 5.7 and 5.8 months for gefitinib and paclitaxel/carboplatin, respectively, approximately coinciding with crossing of the Kaplan-Meier curves. The 12-month progression-free survival rates were 24.9% with gefitinib and 6.7% with paclitaxel/carboplatin.

**Figure 1: Progression-free Survival (ITT Population)**

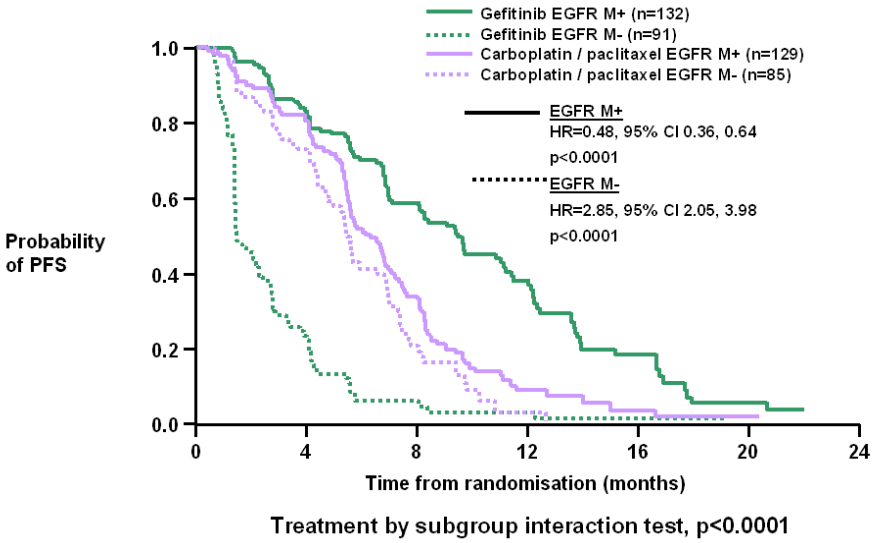



**PFS based on EGFR-TK Mutation Status**

Consent for biomarker analyses was provided by 1038 patients (85%), 683 patients (56%) provided samples, and evaluable EGFR-TK mutation data were available for 437 patients (36%). Patients with an evaluable tissue sample shared similar demographics with the overall population (Appendix 6). Of the 437 samples, 60% (261) were M+ (53.6%[140/261] of these had exon 19 deletions, 42.5% [111/261] exon 21 L858R, 4.2% [11/261] exon 20 T790M, and 3.8% [10/261] other mutations; 11 patients had multiple mutations). The proportions of mutations were well balanced in the two groups (Appendix 6).

For progression-free survival, the interaction test of treatment by EGFR-TK mutation was statistically significant (P<0.0001), indicating that EGFR-TK mutation status is a strong predictive biomarker for the efficacy of gefitinib compared to paclitaxel/carboplatin (Figure 2).

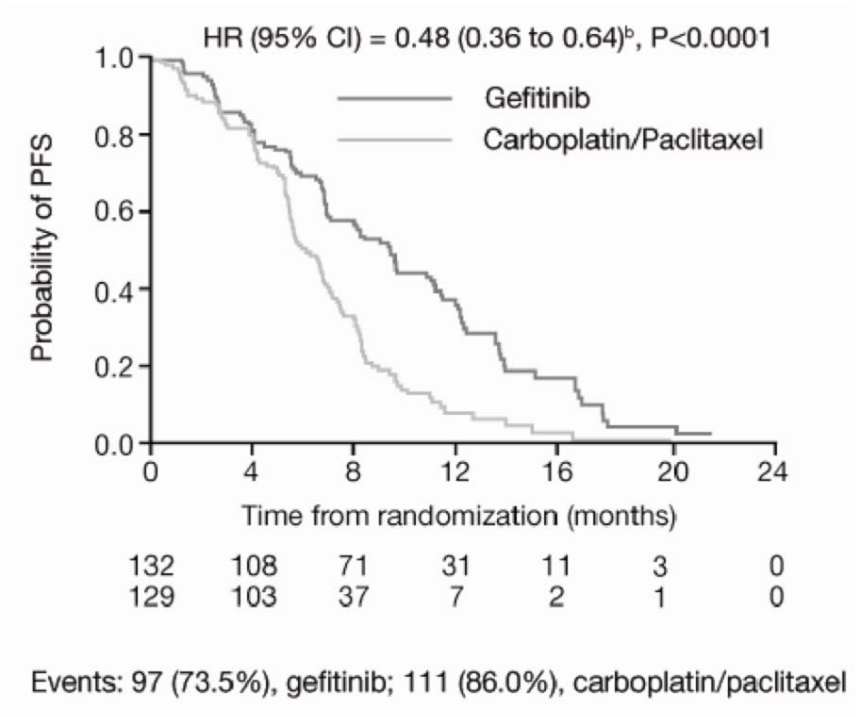
**Figure 2: Progression-free Survival (ITT Population)**




## PFS in EGFR-TK M+ Population

Progression-free survival was significantly longer with gefitinib than paclitaxel/carboplatin in the M+ subgroup (HR 0.48, 95% CI 0.36 to 0.64, P<0.0001) clearly demonstrating the superiority of gefitinib over paclitaxel/carboplatin in EGFR-TK M+ patients for PFS (Figure 3). Median progression free survival was significantly longer for gefitinib-treated patients (9.5 months) compared to patients treated with doublet chemotherapy (6.3 months, p< 0.0001).

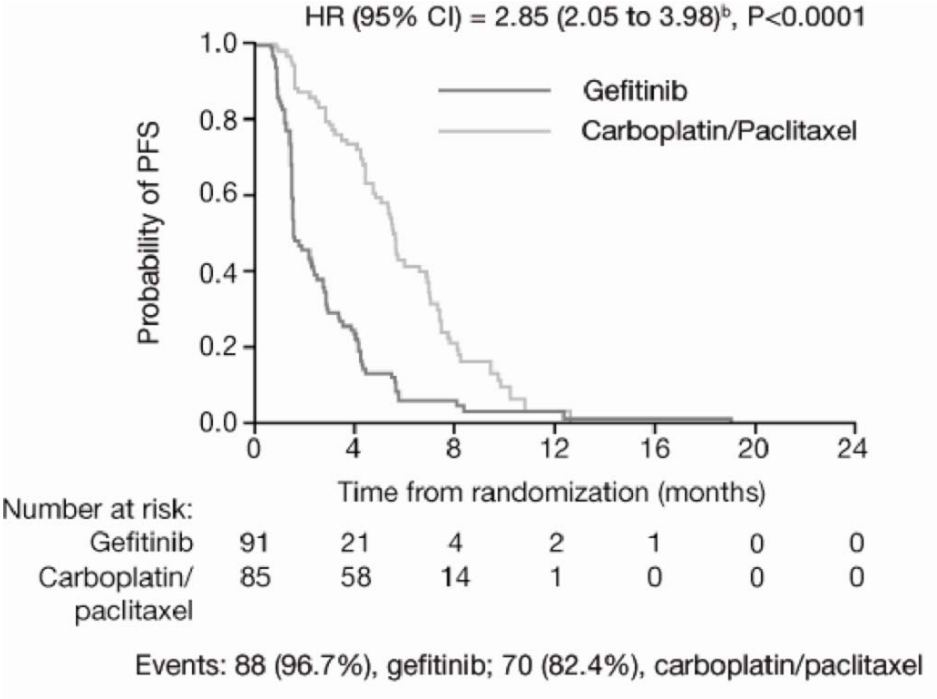
**Figure 3: Progression-free Survival in EGFR-TK M+ Patients**



### PFS in EGFR-TK M- Population

Progression-free survival was significantly shorter with gefitinib than paclitaxel/carboplatin in the M- subgroup (HR 2.85, 95% CI 2.05 to 3.98, P<0.0001) demonstrating that patients with EGFR-TK M- tumours gain greater benefit in PFS on paclitaxel/carboplatin than on gefitinib (Figure 4).

**Figure 4: Progression-free Survival in EGFR-TK M- Patients**




Results in the mutation-unknown subgroup (HR 0.68, 95% CI 0.58 to 0.81, P<0.0001) were similar to those for the overall population.

Median PFS for gefitinib in EGFR-TK M+ patients (the population at which the technology is targeted for) was 9.5 months whilst the median PFS for paclitaxel/carboplatin in the EGFR-TK M+ population (the population for which the standard of care in the UK is currently doublet chemotherapy) was 6.3 months.

### Secondary Endpoints

### Tumour Response Rates

### ORR in ITT Population

The objective response rate (ORR) in the overall population was significantly higher for gefitinib than paclitaxel/carboplatin (43.0% versus 32.2%, OR 1.59, 95% CI 1.25 to 2.01, P=0.0001) (Table 2), and numerically or statistically greater for gefitinib in all clinical subgroups.

**ORR in EGFR-TK M+ Population**

ORR was 71.2% and 47.3% for gefitinib and paclitaxel/carboplatin, respectively, in the M+ subgroup (P=0.0001) (Table 2)

**ORR in EGFR-TK M- Population**

ORR was 1.1% (one patient) and 23.5%, respectively, in the M- subgroup (P=0.0013) (Table 2).

**ORR in EGFR-TK M Unknown Population**

The ORR in patients with unknown EGFR-TK mutation status mirrored those observed in the ITT population (Table 2).

**Table 2: Best Overall Response in the Overall Population, EGFR-TK M+ Patients, EGFR-TK M- Patients, and Patients with Unknown EGFR-TK Mutation Status (Intent-to-Treat Population).**

| Number (%) of Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Overall Population** | | EGFR-TK M+ | | **EGFR-TK M-** | | **Unknown EGFR-TK Mutation** | |
| | | | Patients | | **Patients** | | **Status** | |
| | Gefitinib | Paclitaxel /Carboplatin | Gefitinib | Paclitaxel /Carboplatin | Gefitinib | Paclitaxel /Carboplatin | Gefitinib | Paclitaxel /Carboplatin |
| | (n=609) | (n=608) | (n=132) | (n=129) | (n=91) | (n=85) | (n=386) | (n=394) |
| **Best Overall Response** | | | | | | | | |
| **CR** | 5 (0.8) | 1 (0.2) | 3 (2.3) | 1 (0.8) | 0 | 0 | 2 (0.5) | 0 |
| **PR** | 257 (42.2) | 195 (32.1) | 91 (68.9) | 60 (46.5) | 1 (1.1) | 20 (23.5) | 165 (42.7) | 115 (29.2) |
| **SD** | 182 (29.9) | 286 (47.0) | 27 (20.5) | 52 (40.3) | 35 (38.5) | 51 (60.0) | 120 (31.1) | 183 (46.4) |
| **PD** | 129 (21.2) | 70 (11.5) | 10 (7.6) | 14 (10.9) | 47 (51.6) | 10 (11.8) | 72 (18.7) | 46 (11.7) |
| **Not Evaluable** | 36 (5.9) | 56 (9.2) | 1 (0.8) | 2 (1.6) | 8 (8.8) | 4 (4.7) | 27 (7.0) | 50 (12.7) |
| **Objective Tumor Response (CR+PR)** | 262 (43.0) | 196 (32.2) | 94 (71.2) | 61 (47.3) | 1 (1.1) | 20 (23.5) | 167 (43.3) | 115 (29.2) |
| **Disease Control (CR+PR+SD)** | 444 (72.9) | 482 (79.2) | 121 (91.7) | 113 (87.6) | 36 (39.6) | 71 (83.5) | 287 (74.4) | 298 (75.6) |
| **Analysis of Objective Tumor Response** | | | | | | | | |
| **Odds Ratio (95% CI)** | 1.59 (1.25 to 2.01) | | 2.75 (1.65 to 4.60) | | 0.04 (0.01 to 0.27) | | 1.88 (1.39 to 2.53) | |
| p-value | 0.0001 | | 0.0001 | | 0.0013 | | <0.0001 | |

| Number (%) of Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Overall Population** | | EGFR-TK M+ | | **EGFR-TK M-** | | **Unknown EGFR-TK Mutation** | |
| | | | Patients | | **Patients** | | **Status** | |
| | Gefitinib | Paclitaxel /Carboplatin | Gefitinib | Paclitaxel /Carboplatin | Gefitinib | Paclitaxel /Carboplatin | Gefitinib | Paclitaxel /Carboplatin |
| | (n=609) | (n=608) | (n=132) | (n=129) | (n=91) | (n=85) | (n=386) | (n=394) |
| **Progression Free Survival** | | | | | | | | |
| Median PFS (months) | 5.7 | 5.8 | 9.5 | 6.3 | 1.5 | 5.5 | 6.6 | 5.8 |
| HR (95% CI) | 0.74 (0.65-0.85) | | 0.48 (0.36-0.64) | | 2.85 (2.05-3.98) | | 0.68 (0.58-0.81) | |
| p value | <0.0001 | | <0.0001 | | <0.0001 | | p<0.0001 | |
| **Overall Survival** | | | | | | | | |
| Median OS (months) | 18.6 | 17.3 | NR | 19.5 | 12.1 | 12.6 | 18.6 | 16.9 |
| HR (95% CI) | 0.91 (0.76-1.10) | | 0.78 (0.50-1.20) | | 1.38 (0.92-2.09) | | 0.858 (0.677-1.089) | |
| p value | - | | - | | - | | - | |

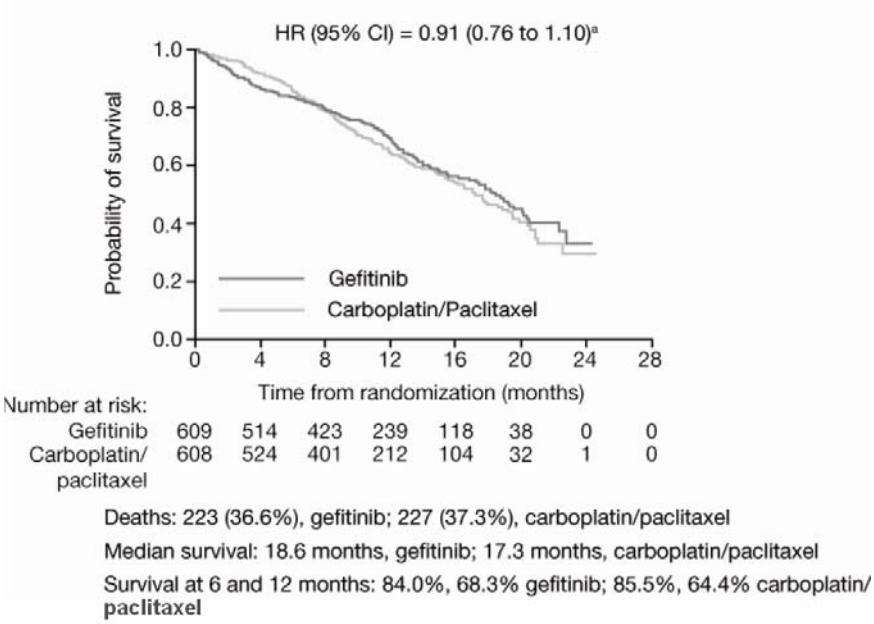
EGFR-TK, epidermal growth factor receptor tyrosine kinase; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval, NR, not reached

**Overall Survival**

Overall survival in this early analysis (450 deaths, 37% maturity, follow-up ongoing) was similar for both groups in the overall population (HR 0.91, 95% CI 0.76 to 1.10). Median survival was 18.6 months with gefitinib and 17.3 months with paclitaxel /carboplatin.

This early analysis is based on a relatively small number of events and follow-up for overall survival is ongoing.

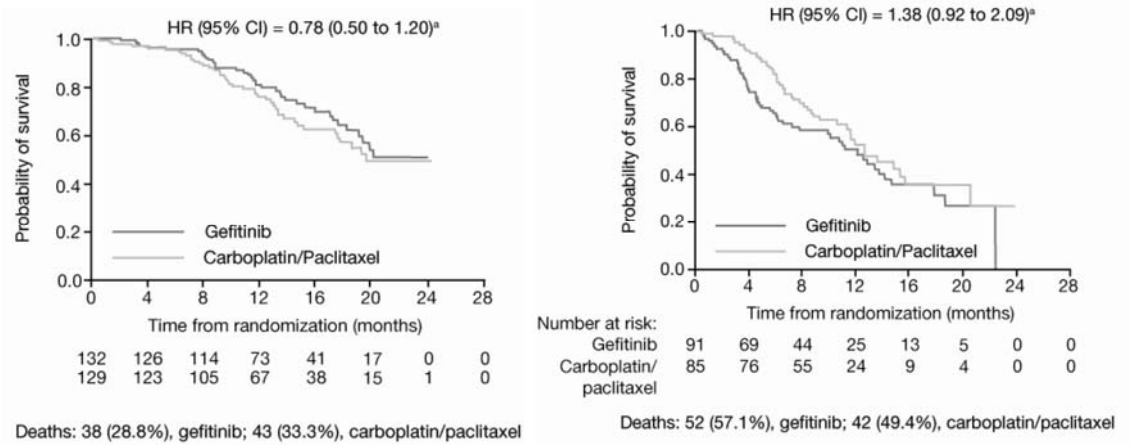
**Figure 5: Overall Survival (ITT Population)**




[a]Cox analysis with covariates (performance status [0-1, 2], smoking history [never, ex-smoker], and gender).
EGFR, epidermal growth factor receptor; OS, overall survival; HR, hazard ratio; CI, confidence interval.

After observing the progression-free survival results, an exploration of overall survival by mutation status was performed, although this included only 81 events in the M+ subgroup and 94 in the M- subgroup. The HRs were 0.78 (95% CI 0.50 to 1.20) in the M+ subgroup, favouring numerically gefitinib and 1.38 (95% CI 0.92 to 2.09) in the M- subgroup favouring numerically doublet chemotherapy (Figures. 6A and 6B).

**Figure 6**: Overall Survival (M+ (A) and M- (B) Patients)
A B

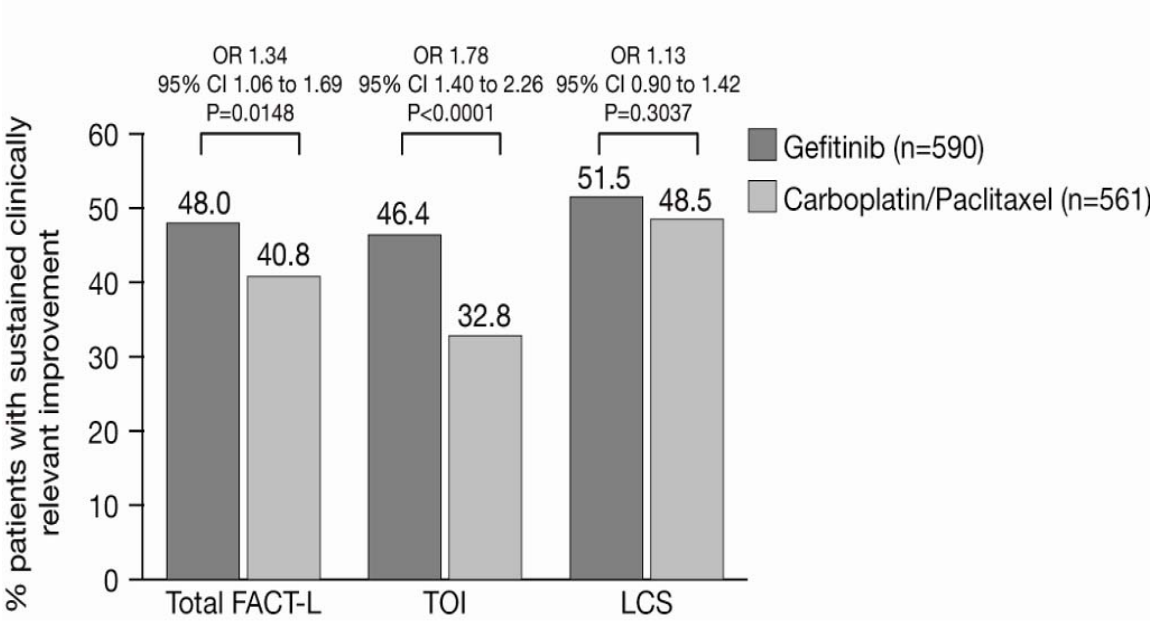



[a]Cox analysis with covariates (performance status [0-1, 2], smoking history [never, ex-smoker], and gender).
EGFR, epidermal growth factor receptor; OS, overall survival; HR, hazard ratio; CI, confidence interval.

**Health-related quality of life (EFQ Population)**

In the ITT population significantly more gefitinib-treated patients had a clinically relevant improvement in health-related quality of life (HRQoL) compared with patients who received paclitaxel/carboplatin (FACT-L: OR 1.34, 95% CI 1.06 to 1.69, P=0.0148; TOI: OR 1.78, 95% CI 1.40 to 2.26, P<0.0001) (Figure 7). Symptomatic improvement rates (as measured by LCS) were similar for gefitinib and paclitaxel/carboplatin in the ITT population (OR 1.13, 95% CI 0.90 to 1.42, P=0.3037) (Figure 7).

**Figure 7 Health-related quality of life Improvements (EFQ Population)**




Results by mutation status are in Figure 8.

**Health-related quality of life in EGFR-TK M+ and EGFR-TK M- Populations**

Analysis of HRQoL based on biomarker status demonstrated that improvements in HRQoL and disease symptoms were also dependant on EGFR-TK mutation biomarker status.

**Health-related quality of life in EGFR-TK M+**

In the EGFR-TK M+ population significantly more gefitinib-treated patients experienced clinically relevant improvements in HRQoL and disease symptoms compared to those patients who received paclitaxel/carboplatin (FACT-L: OR 3.01, 95% CI 1.79-5.07, p < 0.0001; TOI: OR 3.96, 95% CI 2.33-6.71, p < 0.0001; LCS: OR 2.70, 95% CI 1.58-4.62, p = 0.0003) (Figure 8).

Times to worsening in HRQoL (as measured by FACT-L and TOI) and disease-related symptoms (as measured by LCS) were substantially longer in the gefitinib arm compared with the paclitaxel/carboplatin arm in patients with

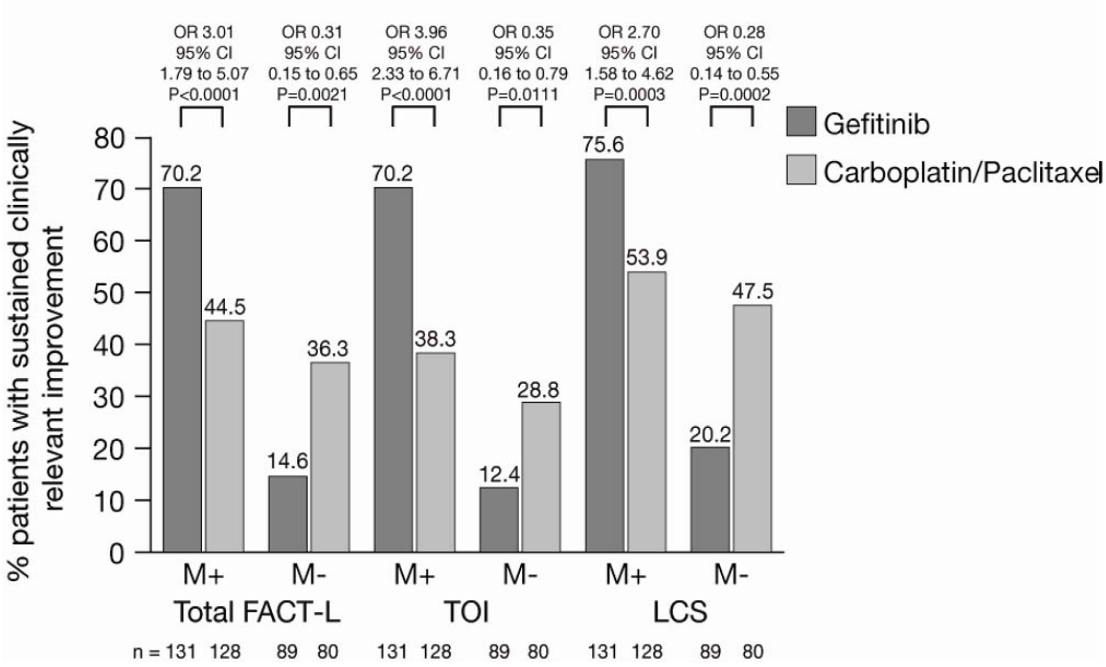
EGFR-TK M+ status (range in medians of 11.3 to 16.6 months with gefitinib and 2.9 to 3.0 months with paclitaxel/carboplatin).

**Health-related quality of life in EGFR-TK M-**

In contrast to the EGFR M+ population, the EGFR-TK M- population had results for FACT-L, TOI and LCS which were significantly in favour of paclitaxel/carboplatin. Significantly more paclitaxel/carboplatin-treated patients experienced clinically relevant improvements in health-related quality of life (HRQoL) and disease symptoms compared to those patients who received gefitinib (FACT-L: OR 0.31, 95% CI 0.15-0.65, p = 0.0021; TOI: OR 0.35, 95% CI 0.16-0.79, p = 0.00111; LCS: OR 0.28, 95% CI 0.14-0.55, p = 0.0002) (Figure 8).

Times to worsening in HRQoL (FACT-L and TOI) and disease related symptoms related symptoms (as measured by LCS) were similar or shorter in the gefitinib arm compared with the paclitaxel/carboplatin arm in patients with EGFR-TK M- status (median of 1.4 months with gefitinib and 1.4 to 4.2 months with paclitaxel/carboplatin).

**Figure 8: Health-related Quality of life Improvements by EGFR-TK mutation status**




The outcomes in HRQoL and disease symptom improvement based on biomarker status clearly reflect the efficacy outcomes for PFS and ORR where patients who were EGFR-TK M+ derived greater benefit from receiving gefitinib and patients who were EGFR-TK M- derived greater benefit from receiving paclitaxel/carboplatin.

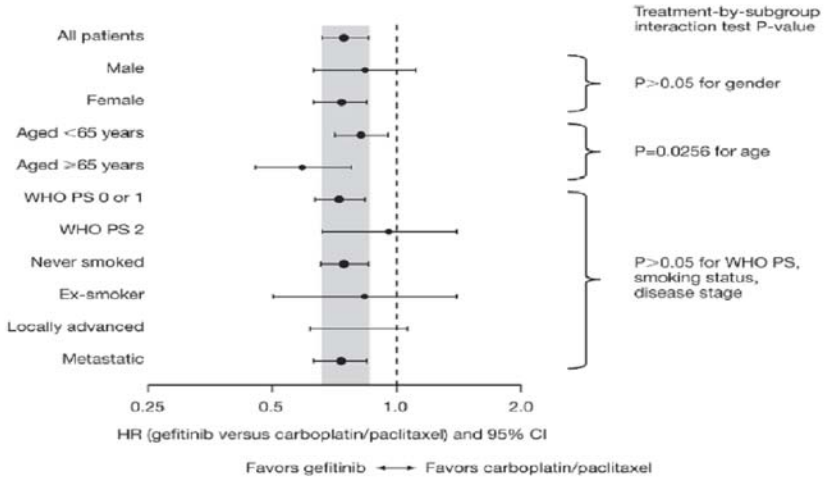
Considering that patients with advanced/metastatic NSCLC have a relatively poor prognosis with only 21.4% of men and 21.8% of women with lung cancer were alive one year after diagnosis, and less than 1% of advanced NSCLC patients were alive after five years [3,4] the efficacy benefits provided by gefitinib over paclitaxel/carboplatin together with the associated improvements in HRQoL and disease symptoms (based on EGFR-TK mutation biomarker status) become increasingly more relevant and further emphasise that the technology should be used in the right patient pool who is likely to derive the greatest benefit i.e. NSCLC patients with EGFR-TK M+ tumours.

**Planned Subgroup Analyses**

Planned subgroup analyses were conducted comparing progression-free survival between treatments in groups defined by WHO performance status, smoking history, gender, age at randomisation and disease stage at screening.

In all subgroups, PFS was statistically or numerically longer with gefitinib compared with paclitaxel/carboplatin treatment (Figure 9). All differences in subgroups were driven (most likely) by the mutation status of the patients, including clinical and molecular characteristics

**Figure 9: Analysis of PFS by subgroup (ITT Population)**




**INTEREST Study**

The efficacy benefits for gefitinib compared to doublet chemotherapy observed in IPASS are supported by other studies. These studies demonstrate that gefitinib has high anti-tumour activity in EGFR-TK M+ patients.

The INTEREST study was a randomised open label phase III study in patients with stage IIIB/IV NSCLC who had progressive or recurrent disease, had

received 1 or 2 prior chemotherapy regimens (with at least one being a platinum-based regimen) and were eligible for further chemotherapy with docetaxel. 1466 patients were randomised on a 1:1 basis to receive either gefitinib 250mg once daily as an oral tablet or docetaxel 75mg/$m^2$ i.v once every 3 weeks. In EGFR-TK M+ patients, PFS (Figure 10) and ORR (Figure 11) with gefitinib are significantly greater than singlet chemotherapy in pre-treated non-Asian patients[14].

In pre-treated EGFR-TK M+ patients in the INTEREST study, gefitinib was superior to docetaxel in terms of PFS (HR 0.16, 95% CI 0.05 to 0.49, p=0.0012) and ORR (42.1% versus 21.1%, p=0.0361).

Based on the evidence from Phase III studies it can be concluded that EGFR-TK mutation status is a strong predictive biomarker for differential efficacy benefit with gefitinib.

**Other Phase III Studies**

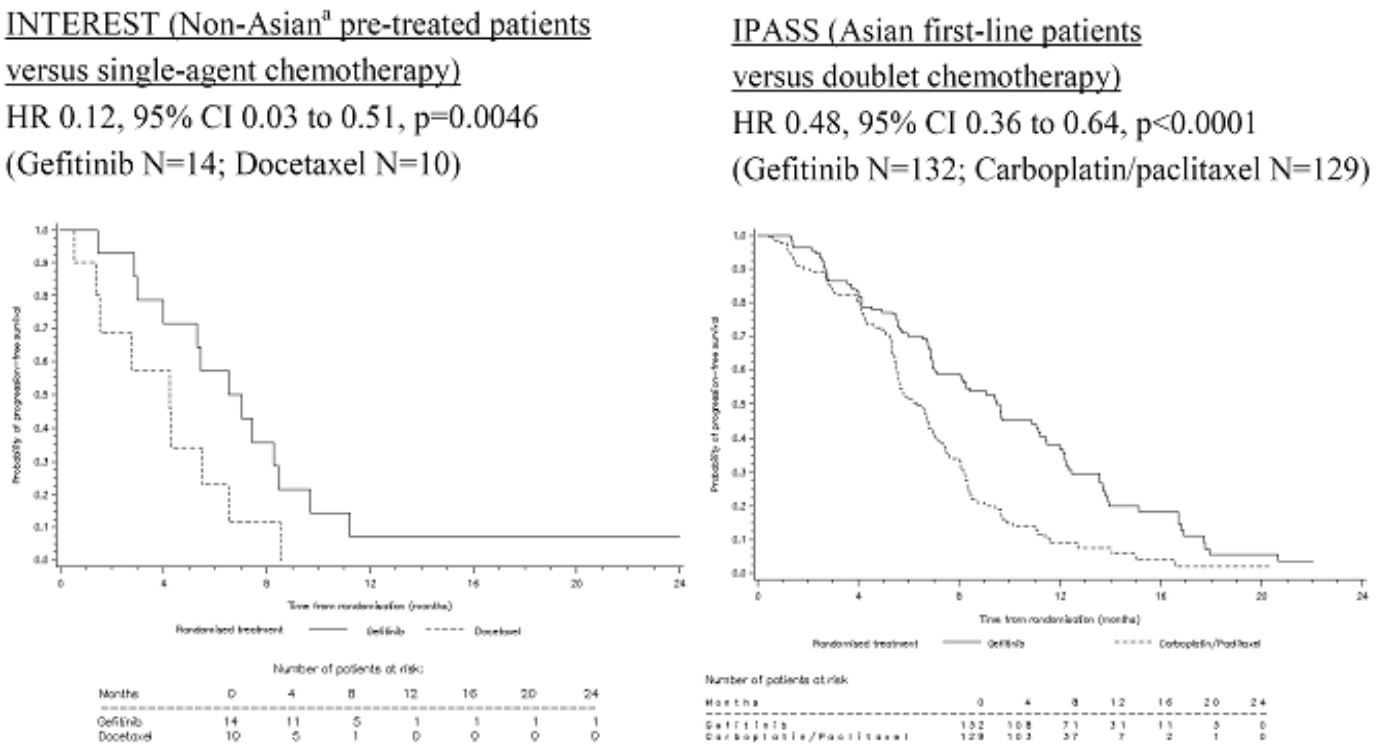
The positive efficacy outcomes demonstrated in EGFR-TK M+ patients in IPASS and INTEREST have been confirmed by recently presented data[20,21].

The North East Japan Gefitinib Study Group compared gefitinib to paclitaxel/carboplatin in EGFR-TK M+ patients as first line treatment of NSCLC. Analysis demonstrates that gefitinib has a superior PFS compared to paclitaxel/carboplatin (median PFS 10.4 vs. 5.5 months respectively, HR=0.357, 95%CI:0.25 – 0.51, p<0.001 - Kobayashi et al 2009 – Figure 12A). This was a pre-planned interim analysis and the data was so strongly supportive of Iressa efficacy that the data monitoring committee recommended that recruitment to the trial should stop, as convincing efficacy had already been demonstrated.

The First-SIGNAL study evaluated gefitinib versus gemcitabine/cisplatin in first line NSCLC in never smokers with adenocarcinoma, similar to the population in IPASS[21]. In the EGFR TK M+ subgroup of this study, a 63% improvement in PFS for gefitinib over gemcitabine/cisplatin was observed (HR (95%CI)= 0.613 (0.308 to 1.221) p=0.084 – Figure 12B), but this was not statistically significant probably due to the small number of EGFR-TK M+ patients in this subgroup (n=42).

Further discussion of First-SIGNAL study and the North East Japan Gefitinib Study Group are discussed below in the meta-analysis (see section 6.5)

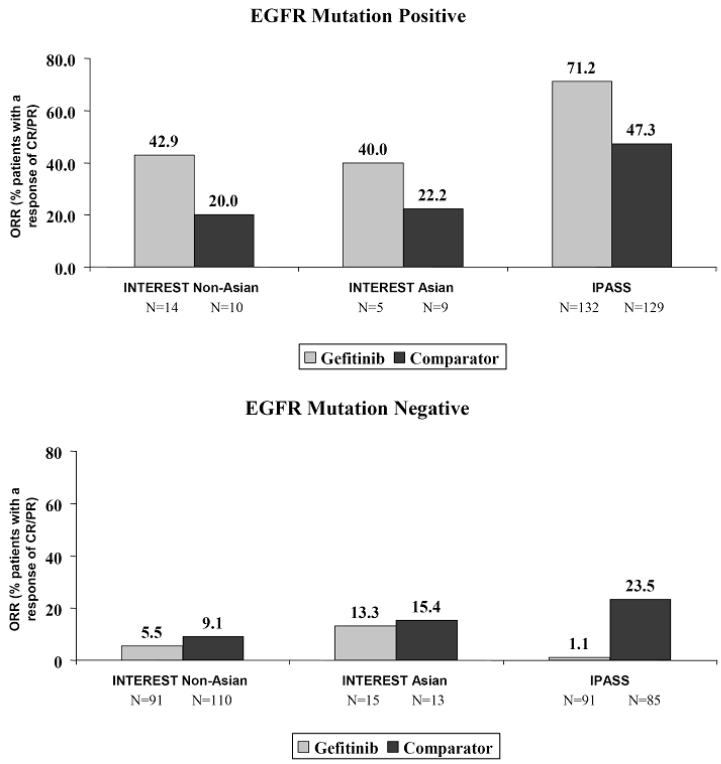
**Figure 10: Progression-free survival probability for EGFR-TK M+ patients: INTEREST and IPASS**



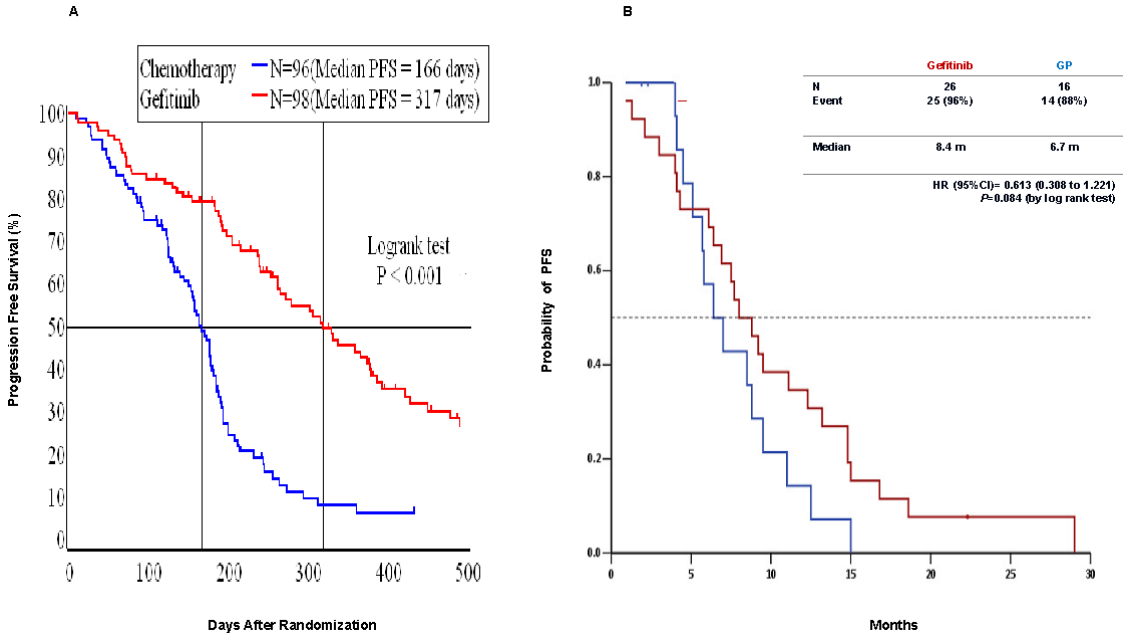

a Ethinicities included in INTEREST Non-Asian Group: 20 Caucasian, 3 Black, 1 other

Note that within the EGFR M+ subgroups of both INTEREST and IPASS key demographic and baseline characteristics were well balanced across the two treatment groups, therefore the treatment effect is not driven by differenced in demographic characteristics.

## Figure 11: Summary of objective response rates according to EGFR-TK mutation status in INTEREST and IPASS




## Figure 12: PFS Outcomes in Phase III trials of Gefitinib vs Doublet Chemotherapy as First Line Therapy for EGFR-TK M+ NSCLC Patients



## *6.5 Meta-analysis*

### INTRODUCTION

During the late stage of the production of this Single Technology Appraisal, two randomised controlled trials comparing gefitinib to doublet chemotherapy for the treatment of chemotherapy naïve patients with aNSCLC were brought to our attention[20,21] in addition to the IPASS trial[9]. The First-SIGNAL trial[21] was presented at the recent World Lung Cancer Conference (San Francisco, USA from 31 July to 4 August 2009) and the North East Japan Gefitinib Study Group trial[20] was presented at the American Society of Clinical Oncology Annual Meeting (Orlando, USA from 29 May to 2 June 2009).

### DESCRIPTION OF TRIALS

The First-SIGNAL trial[21], as discussed previously, investigated gefitinib compared to gemcitabine/cisplatin in first-line aNSCLC in never smokers with adenocarcinoma. While this is a similar patient population to IPASS, the number of patients that would be appropriate to receive gefitinib within its marketing authorization is very small (EGFR-TK M+ population, n=42). In addition, this trial compares gefitinib with a different comparator than IPASS and so would be unsuitable for meta-analysis, unless it was assumed that all doublet chemotherapies are the same. As the remit of this submission does not make that assumption we have limited the meta-analyses conducted here to the same comparators.

The North East Japan Gefitinib Study Group trial[20] is being conducted independent of AstraZeneca and so only limited information was available at the time of this submission. Based on this limited information a critical appraisal of the trial can be found in **Table 3** with pertinent patient demographic details listed in **Table 4**.

Based on the available information, the North East Japan Gefitinib Study Group trial[20] would appear to be similar enough to the IPASS trial[9] to warrant combination of the results by meta-analysis. The available efficacy results presented in the abstract/poster of the North East Japan Gefitinib Study Group trial are presented below:

Progression-free survival (PFS) – the trial demonstrates that gefitinib has superior PFS compared to paclitaxel/carboplatin (Hazard Ratio [HR] 0.357, 95% CI: 0.25 to 0.51, $p<0.001$);

Objective response (a combination of complete and partial response) - the trial demonstrates that gefitinib has a superior OR compared to paclitaxel/carboplatin (74.5% vs 29.0%, $p<0.001$).

**Table 3.** Critical appraisal of the North East Japan Gefitinib Study Group trial[20]

| Criteria for Critical Appraisal | North East Japan Gefitinib Study Group trial |
|---|---|
| How was allocation concealed? | Open-label |
| What randomisation technique was used? | Randomised 1:1 ratio, balanced for institution, sex, and stage |
| Was a justification of the sample size provided? | Sample size was calculated for progression-free survival to demonstrate superiority of gefitinib vs paclitaxel/carboplatin (hazard ratio 0.69, alpha = 5%, power = 80%) |
| Was follow-up adequate? | Only an interim analysis of PFS is available, that was pre-specified 4 months after 200 patients had entered the trial. A subsequent analysis is planned to take place later in 2009 |
| Were the individuals undertaking the outcomes assessment aware of allocation? | Yes |
| Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely. | Parallel group |
| Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice? | No – the trial took place in multiple centres in Japan. |
| How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting. | The trial was conducted in Japanese patients with aNSCLC that were EGFR-TK mutation positive, were chemo-naïve, performance status 0-1, aged 20-75 years |
| For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics? | Gefitinib: 250mg once daily<br><br>Paclitaxel (200mg/m$^2$)/Carboplatin (AUC 6) on day 1 every 3 weeks |
| Were the study groups comparable? | Demographic characteristics appear to be well-balanced between groups, although slightly fewer patients were non-smokers in the doublet chemotherapy arm compared to the gefitinib arm (58% vs 65%) but slightly more patients adenocarcinoma (96% vs 88%) and with less advanced NSCLC (stage IIIB 18% vs 11%) in the doublet chemotherapy arm compared to the gefitinib arm |
| Were the statistical analyses used appropriate? | No details provided |
| Was an intention-to-treat analysis undertaken? | No details provided |
| Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)? | No |

**Table 4.** Patient characteristics in the North East Japan Gefitinib Study Group trial[20]

| **Kobayashi 2009** | **Gefitinib (n=98)** | **Paclitaxel/Carboplatin (n=100)** |
|---|---|---|
| Age (SD) | Mean 63.4 (7.8) | Mean 62.8 (8.7) |
| Gender (% male) | 56 (80%) | 46 (66%) |
| Ethnicity<br>- Caucasian<br>- Oriental<br>- Other | Not reported<br>(assumed 100% Oriental) | Not reported<br>(assumed 100% Oriental) |
| Smoking history<br>- non-smoker<br>- current smoker | 64 (65.3%)<br>34 (34.7%) | 58 (58.0%)<br>42 (42.0%) |
| Performance status<br>- 0<br>- 1<br>- 2 | 48 (49.0%)<br>49 (50.0%)<br>1 (1.0%) | 49 (49.0%)<br>49 (49.0%)<br>2 (2.0%) |
| Tumour histology<br>- adenocarcinoma<br>- large cell carcinoma<br>- adenosquamous carcinoma<br>- squamous cell carcinoma<br>- other | 88 (89.8%)<br>1 (1.0%)<br>2 (2.0%)<br>3 (3.1%)<br>4 (4.1%) | 96 (96.0%)<br>0 (0.0%)<br>1 (1.0%)<br>2 (2.0%)<br>1 (1.0%) |
| Stage classification<br>- IIIB<br>- IV<br>- relapse | 11 (11.2%)<br>77 (78.6%)<br>10 (10.2%) | 18 (18.0%)<br>75 (75.0%)<br>7 (7.0%) |
| EGFR mutations<br>- Exon 19 deletion<br>- L858R<br>- Others | 50 (51.0%)<br>43 (43.9%)<br>5 (5.1%) | 50 (50.0%)<br>43 (43.0%)<br>7 (7.0%) |

The relevant grade 3/4 adverse events that will be used in the health economic evaluation are presented in **Table 5**.

**Table 5.** Number of patients experiencing a grade 3/4 adverse event in the North East Japan Gefitinib Study Group trial[20] that are required for the health economic evaluation

| **Grade 3/4 Adverse Event** | **Gefitinib (n=98)** | **Paclitaxel/Carboplatin (n=99)** |
|---|---|---|
| Anaemia | 0 | 6 |
| Diarrhoea | 1 | 0 |
| Fatigue | 3 | 1 |
| Febrile Neutropenia | NR | NR |
| Nausea and Vomiting | NR | NR |
| Neutropenia | 1 | 33 |
| Rash | 5 | 3 |

NR = not reported

Other grade 3/4 adverse events presented in the abstract/poster are: alopecia 0 vs 0, appetite loss 6 vs 5, arthralgia 1 vs 8, constipation 0 vs 1, nail changes 2 vs 0, neuropathy: sensory 0 vs 5, pneumonitis 2 vs 0, AST/ALT 24 vs 1,

creatinine 0 vs 0, leukocytopenia 0 vs 28, thrombocutopenia 0 vs 3 for gefitinib vs paclitaxel/carboplatin, respectively. However, these adverse events were not combined in a meta-analysis, as they will not be carried forward into the health economic evaluation.

## METHODS

The meta-analyses conducted employed a fixed effects model as the primary analysis and random effects model as a sensitivity analysis. This is because a fixed effects model gives more weight to larger trials rather than more evenly weighting trials as in a random effects model, which could give undue weight to small trials with extreme results[22].

The meta-analysis of PFS used the generic inverse variance method[23], while the meta-analyses of objective response and grade 3/4/5 adverse events used the odds ratio as the summary estimate with the Mantel-Haenszel method employed for fixed effects[24] and the method developed by DerSimonian and Laird for random effects[25].

## RESULTS

The results of the meta-analysis of PFS are presented in **Figure 13**. They are broadly similar for the fixed effects model (HR 0.43, 95% CI: 0.34 to 0.53) and random effects model (HR 0.42, 95% CI: 0.32 to 0.56). Gefitinib is significantly more effective than paclitaxel/carboplatin (p<0.00001, for both models). No significant heterogeneity was detected (p=0.21) and there was low inconsistency in trial results ($I^2$=37.6%)[26].

The results for objective response are presented in **Figure 14**. Again, the results are similar for the fixed effects model (OR 4.04, 95% CI: 2.73 to 5.98) and random effects model (OR 4.36, 95% CI: 1.72 to 11.09), despite significant heterogeneity and high inconsistency of trial results (p=0.02 and $I^2$=81.2%, respectively). Gefitinib has significantly higher objective response compared to paclitaxel/carboplatin (p<0.00001 and p=0.002, respectively). The limited information available on the North East Japan Gefitinib Study Group trial limited our ability to make any assessment of the potential cause of the significant heterogeneity detected.

The results for the meta-analyses of grade 3/4/5 adverse events are summarised in **Table 6** with supporting figures presented in section 10.7 **Appendix 7.**

**Table 6.** Results of the meta-analyses of grade 3/4/5 adverse events from the IPASS trial[27] and the North East Japan Gefitinib Study Group trial[20] (Odds Ratio [OR]<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Adverse Event (Grade 3/4/5) | Mean Odds Ratio | 95% Confidence Interval | | p-value | Heterogeneity Statistics |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| Anaemia | | | | | |
| - Fixed Effects | 0.12 | 0.03 | 0.47 | 0.002 | $Chi^2$=0.19, p=0.66 |
| - Random Effects | 0.13 | 0.03 | 0.49 | 0.003 | $I^2$=0% |
| Diarrhoea | | | | | |
| - Fixed Effects | 5.78 | 1.01 | 33.11 | 0.05 | $Chi^2$=0.19, p=0.66 |
| - Random Effects | 5.55 | 0.95 | 32.36 | 0.06 | $I^2$=0% |
| Fatigue | | | | | |
| - Fixed Effects | 0.77 | 0.19 | 3.13 | 0.72 | $Chi^2$=2.73, p=0.10 |
| - Random Effects | 0.75 | 0.03 | 16.42 | 0.86 | $I^2$=63.4% |
| Neutropenia | | | | | |
| - Fixed Effects | 0.01 | 0.00 | 0.03 | <0.00001 | $Chi^2$=0.04, p=0.85 |
| - Random Effects | 0.01 | 0.00 | 0.03 | <0.00001 | $I^2$=0%, |
| Rash | | | | | |
| - Fixed Effects | 2.50 | 0.71 | 8.87 | 0.16 | $Chi^2$=0.71, p=0.40 |
| - Random Effects | 2.26 | 0.61 | 8.37 | 0.22 | $I^2$=0%, |

The results of the meta-analyses of grade 3/4/5 adverse events are very similar for the fixed and random effects models (**Table 6**). No significant statistical heterogeneity was detected in any of the comparisons (all p≥0.10 and there was no inconsistency in trial results ($I^2$=0%), with the exception of fatigue, where there was moderate inconsistency ($I^2$=63.4%).

**COMMENT**

Of the three trials available that assess gefitinib compared to doublet chemotherapy for the first-line treatment of aNSCLC [9,20,21], the two trials that were conducted in similar patients and had identical comparators (gefitinib vs paclitaxel/carboplatin) had their results combined by meta-analysis[9,20]. The results of the North East Japan Gefitinib Study Group trial[20] appear to be very consistent with the results from the IPASS.[9].

**Figure 13.** Meta-analysis of progression-free survival for gefitinib compared to paclitaxel/carboplatin (pac/carb) for the first-line treatment of advanced non-small-cell lung cancer (EGFR-TK M+ population)

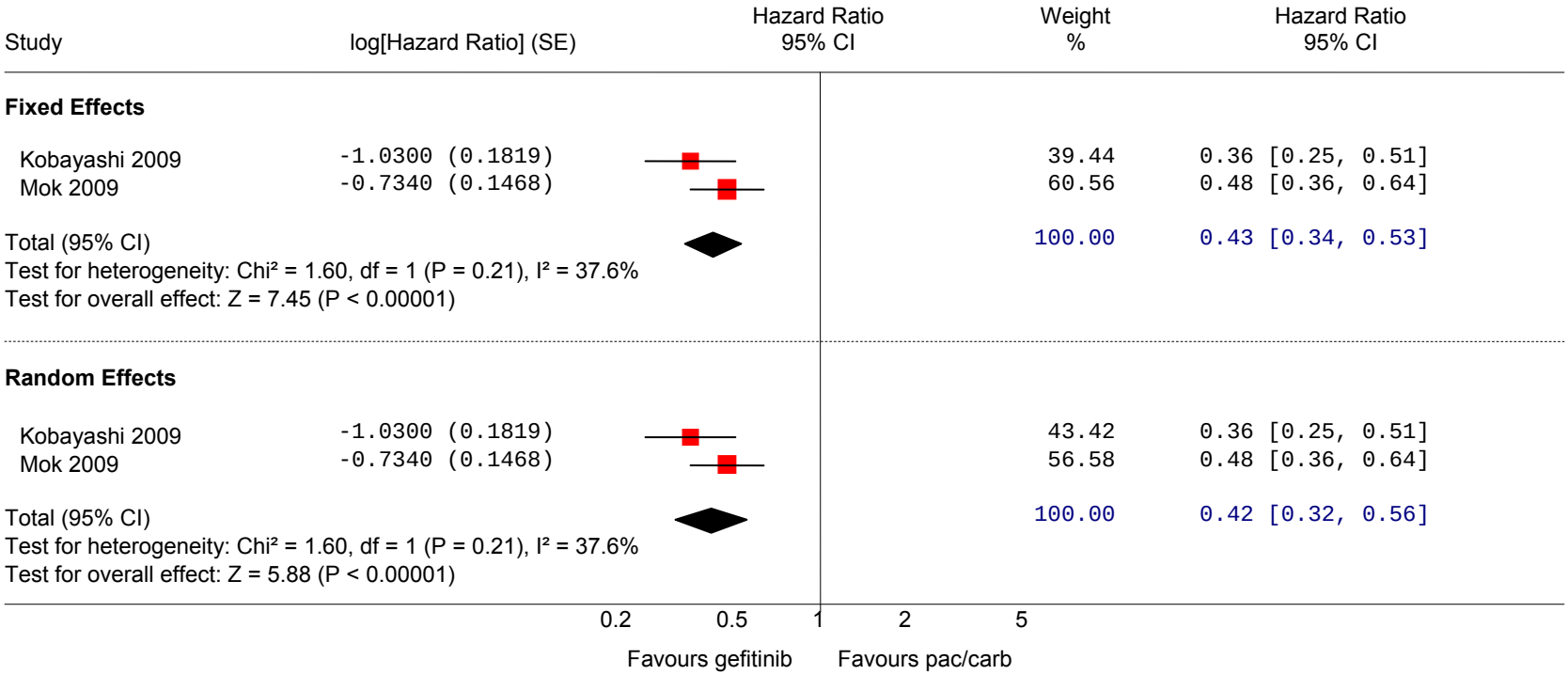
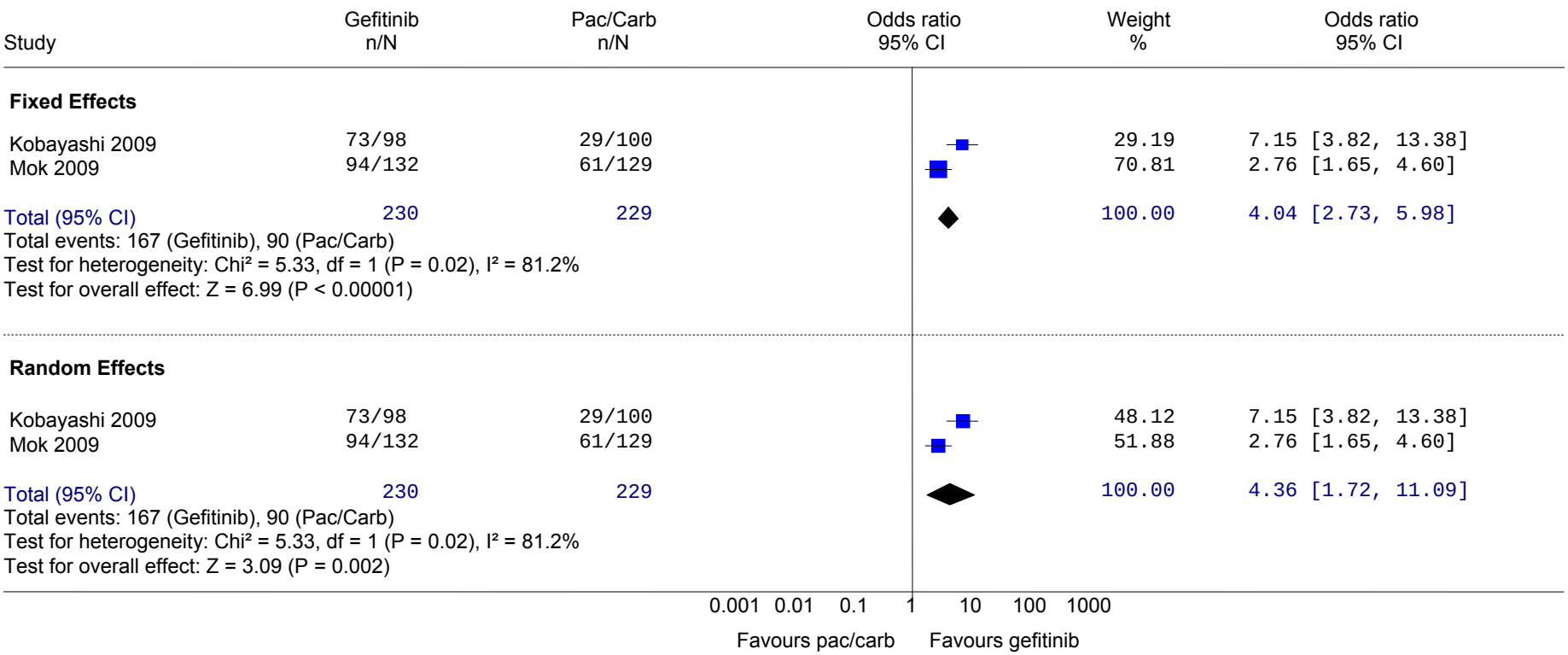


**Figure 14.** Meta-analysis of objective response for gefitinib compared to paclitaxel/carboplatin (pac/carb) for the first-line treatment of advanced non-small-cell lung cancer (EGFR-TK M+ population)



## *6.6 Indirect/mixed treatment comparisons*

### EXECUTIVE SUMMARY

The scope of the technology appraisal includes gefitinib compared with platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine. However, as gefitinib is the first EGFR-TK inhibitor to be licensed for use 1st line in advanced non-small-cell (aNSCLC) lung cancer, there are no other randomised controlled trials in the literature comparing the use of doublet chemotherapies in EGFR-TK M+ patients.

The only trials providing evidence about the use of a doublet chemotherapy in EGFR-TK M+ patients are the IPASS trial[9] and the North East Japan Gefitinib Study Group trial[20], which compared gefitinib to paclitaxel/carboplatin, and the First-SIGNAL trial[21], which compared gefitinib compared to gemcitabine/cisplatin. As presented in section 6.5 (Meta-analysis), meta-analysis was only performed on the two trials that compared identical treatments[9,20] for the following outcomes: progression-free survival (PFS), objective response, and grade 3/4/5 adverse events.

The analysis of IPASS suggests an enhanced response to treatment with paclitaxel/carboplatin in EGFR-TK M+ patients compared to EGFR-TK M- patients, e.g. Table 2 presents median overall survival for paclitaxel/carboplatin in EGFR-TK M+ and M- populations as 19.5 months and 12.6 months, respectively. As such, it may be inappropriate to conduct a mixed treatment comparison (MTC) on a network of trials that contains trials in EGFR-TK M+ patients and additional trials conducted in unselected populations. As such, the following strong assumption was made in order to allow comparisons of doublet chemotherapies with gefitinib: the relative effect of alternative doublet chemotherapies compared to paclitaxel/carboplatin in an unselected aNSCLC population would be obtained. In the health economic evaluation, the relative estimates will be applied to a “baseline” event rate in EGFR-TK M+ patients who received paclitaxel/carboplatin in the IPASS trial. This will give the best estimate of the effect of the alternative doublet chemotherapies in an EGFR-TK M+ population in the absence of these data.

This section will report a systematic review and mixed treatment comparison (MTC) of randomised controlled trials comparing doublet chemotherapies in chemo-naïve patients with aNSCLC using paclitaxel/carboplatin as a baseline for the results.

The systematic review of the literature identified 28 trials appropriate for inclusion in the network that formed the basis for the MTC of doublet chemotherapies. Data was extracted and analysed for efficacy (overall survival, progression-free survival, objective response) and tolerability (anaemia, diarrhoea, fatigue, febrile neutropenia, nausea and vomiting, and neutropenia), for use in the health economic evaluation.

No individual doublet chemotherapy was identified as offering substantial clinical benefit, over the other doublet chemotherapies assessed, in addition to the most favourable tolerability profile. Different chemotherapies were identified as the most effective for each of the efficacy outcomes and the best tolerated for each of the tolerability outcomes. An overall assessment of which treatments are considered to offer the best value to the UK NHS will depend upon the interplay of these different outcomes as assessed within the health economic evaluation.

## INTRODUCTION

The chemotherapy regimens to be compared with gefitinib for the 1st line treatment of aNSCLC lung cancer have been identified as platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine. However, the only trials providing evidence about gefitinib compared to doublet chemotherapy in EGFR-TK M+ patients are the IPASS trial[9] and the North East Japan Gefitinib Study Group trial[20], which compared gefitinib to paclitaxel/carboplatin, and the First-SIGNAL trial[21], which compared gefitinib compared to gemcitabine/cisplatin. In addition, the marketing authorisation for gefitinib specifies its use in patients who are EGFR-TK M+.

In the absence of direct comparison in randomised controlled trials, it is possible to obtain comparable data from an adjusted indirect comparison. Various methodologies have been suggested in the literature but the most valid for decision making have been identified as the adjusted indirect comparison using a common comparator (the “Bucher method”) and the MTC[28]. As eight doublet chemotherapies are required for the current analysis, the MTC was the preferred option as this allows for simultaneous comparison of all of the treatments providing applicable randomised controlled trials can be identified in the literature.

In addition, it was anticipated that there would be no trials identified comparing doublet chemotherapies in an EGFR-TK M+ population, as gefitinib is the first EGFR-TK inhibitor to be licensed for use in 1st line aNSCLC. The following strong assumption was made in order to allow comparisons of doublet chemotherapies with gefitinib:

the relative effect of alternative doublet chemotherapies compared to paclitaxel/carboplatin in an unselected aNSCLC population would be obtained;

in the health economic evaluation, the relative estimates will be applied to a “baseline” event rate in EGFR-TK M+ patients who received paclitaxel/carboplatin in the IPASS trial.

This will give the best estimate of the effect of the alternative doublet chemotherapies in an EGFR-TK M+ population in the absence of these data.

This section will report a systematic review and MTC of randomised controlled trials comparing doublet chemotherapies in chemo-naïve patients with aNSCLC using paclitaxel/carboplatin as a baseline for the results.

In order to identify the appropriate randomised controlled trials for inclusion in the MTC, a systematic review of the literature was performed.

## METHODS

### Literature Searches

For the systematic review, the following bibliographic databases were searched for papers and abstracts in May 2009 with no time restrictions:

Cochrane Central Register of Controlled Trials (CENTRAL) using the Cochrane Library's online clinical trials search;

Excerpta Medica Database (EMBASE) using OVID;

Index Medicus database (MEDLINE), including Medline (R) In-Process, using OVID.

The search strategy was tailored to comply with the searching functionality of each databases, but all included terms related to non-small-cell lung cancer and the doublet chemotherapies under consideration. The systematic review was limited to English-language publications. The search strategies used for each database are shown in section 10.8 Appendix 8.

### Trial Selection

To be eligible for inclusion in the MTC, a trial needed to:

be a randomised controlled trial;

involve patients with locally advanced or metastatic non-small-cell lung cancer;

include patients who had not been treated with prior chemotherapy (first-line patients);

include at least two of the doublet chemotherapies under consideration in the submission.

### Data Extraction

After identifying the relevant papers and abstracts that met the inclusion criteria, the internal validity of each was critically appraised. If the methodological quality of the trial was adequate, data was extracted.

To ensure consistency of the dataset for the outcomes assessed, overall survival, progression-free survival and objective response (complete or partial response) were assessed in the intention-to-treat population.

Data on the following tolerability outcomes (classified as grade 3/4/5 toxicity) were also extracted from the safety population for use in the health economic evaluation: anaemia, diarrhoea, fatigue, febrile neutropenia, nausea and vomiting, and neutropenia.

Data was extracted from the trials as reported – no attempt was made to standardise the definition of outcomes, as these were unavailable for all trials.

### Data Analysis

The MTC was implemented in WinBUGS[29] using a Bayesian MCMC simulation[30], with 100,000 iterations for burn-in to ensure the model had converged on the posterior distribution prior to the results being generated by the subsequent 10,000 updates. Summary estimates for each treatment were calculated as either hazard ratios (for OS and PFS) or odds ratios (for objective response and all tolerability outcomes) compared to the "baseline" treatment of paclitaxel/carboplatin. Bayesian statistical inference provides probability distributions for treatment effect parameters, which can be summarised with 95% credible intervals (95% CrI), rather than 95% confidence intervals. A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in this range.

Which treatment is considered to be the most effective was assessed by the probability of that treatment having the largest beneficial effects, calculated as the proportion of simulations in which the treatment was ranked as "best" according to the relative efficacy for that outcome measure.

Fixed and random effects models were explored and the model that had the lowest Deviance Information Criterion (DIC) was selected for reporting results. DIC measures the fit of the model while penalising for the number of effective parameters[31]. For the chosen model, consistency of the evidence was assessed using the posterior mean residual deviance, which should approximate the number of unconstrained data points in a good-fitting model[32].

## RESULTS

### Trial Flow

Results from the search strategy are presented in **Figure 15**. Of the 28 trials identified, all of them met the inclusion criteria for the mixed treatment comparison[5-7,17,18,33-55]. A summary of the design of the trials included in the MTC can be found in Table 7. The inclusion/exclusion criteria, pertinent demographic information and a critical appraisal of each trial has been provided in section 10.8 **Appendix 8**.

**Figure 15.** Flowchart of trials in the systematic review

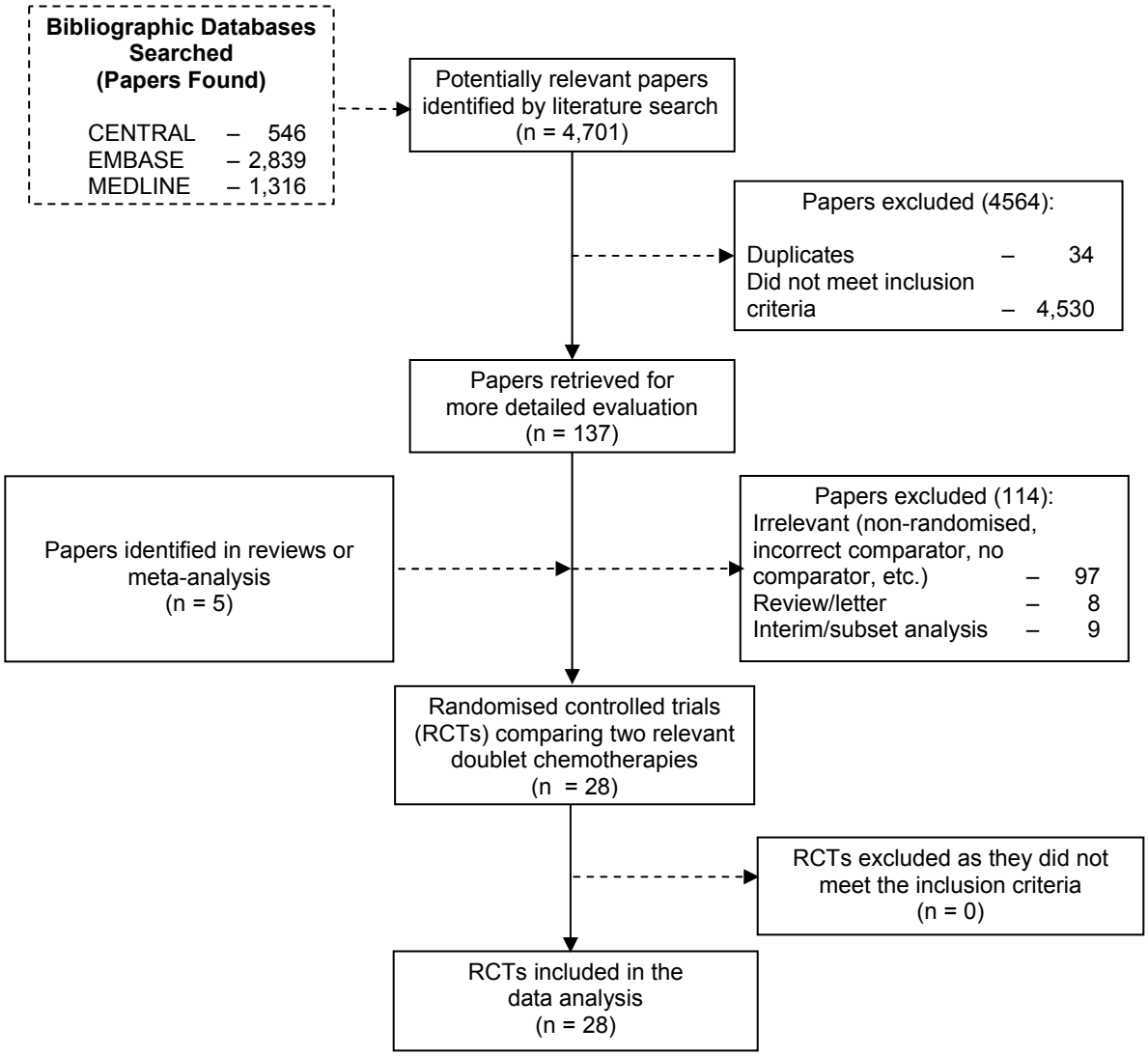


**Table 7.** Randomised controlled trials included in the mixed treatment comparison

| Study ID | Intervention (with dosage) | Comparators (with dosages) | Population (PS = Performance Status) | Primary study reference (abbreviated) |
|---|---|---|---|---|
| Chang 2001 | Vinorelbine (20 mg/m$^2$) on day 1, 8, and 15 plus cisplatin (80 mg/m$^2$) on day 15 | Gemcitabine (1000 mg/m$^2$) on day 1, 8, and 15 plus cisplatin (80 mg/m$^2$) on day 15 | Chemo-naïve Stage IIIb or IV, ECOG PS≤2 | Proc Am Soc Clin Oncol 20: 2001 (abstr 1339) |
| Chen 2004 | Paclitaxel on days 1, 8, and 15 of every 4 weeks plus cisplatin 60 mg m$^{-2}$ iv on day 15 | Vinorelbine on days 1, 8, and 15 of every 4 weeks plus cisplatin 60 mg m$^{-2}$ iv on day 15 | Chemo-naïve Stage IIIb or IV, WHO PS≤2 | Brit J Cancer 2004; 90: 359-65 |
| Chen 2006 | Paclitaxel 160mg/m$^2$ 3h iv plus carboplatin (AUC 6) 1h iv on day 1 every 3 weeks | Paclitaxel 160mg/m$^2$ 3h iv plus cisplatin 60mg/m$^2$ 1h iv on day 1 every 3 weeks | Chemo-naïve, elderly (age ≥70) Stage IIIb or IV, WHO PS≤2 | J Thorac Oncol 2006; 1: 141-5 |
| Chen 2007 | Vinorelbine/Cisplatin (Cisplatin 60mg/m$^2$ iv on day 1 +, Vinorelbine 25mg/m$^2$ on days 1 and 8, of every 3 weeks) | Docetaxel/Cisplatin (Cisplatin 60mg/m$^2$ iv on day 1 + Docetaxel 60mg/m$^2$ on day 1, of every 3 weeks) | Chemotherapy-naïve Stage IIIb or IV, WHO PS≤2 | Chen et al. Lung Cancer 2007; 56: 363-9 |
| Comella 2000 | Cisplatin 100 mg/m$^2$ on day 1 and Gemcitabine 1,000 mg/m2 on day 1, 8, and 15 every 4 weeks | Cisplatin 120 mg/m$^2$ on day 1 and 29 (and then every 6 weeks) and Vinorelbine 30 mg/m$^2$/week for 10 weeks | Chemo-naïve Stage IIIb or IV, ECOG PS≤1 | J Clin Oncol 2000; 18: 1451-7 |
| Douillard 2005 | Docetaxel 75 mg/m$^2$ 1h iv plus Cisplatin 100 mg/m$^2$ 1h infusion on day 1 | Cisplatin 100 mg/m$^2$ 1h infusion on day 1 plus vinorelbine 30 mg/m$^2$ 15 min infusion on days 1 and 8 | Chemo-naïve Stage IV, WHO PS≤2 | Ann Oncol 2005; 16: 81-9 |
| Edelman 2004* | Carboplatin (AUC 5.5) on day 1 plus gemcitabine (1000 mg/m$^2$ days 1 and 8). Repeated every 21 days for three cycles | Cisplatin (100 mg/m$^2$) on day plus vinorelbine (25 mg/m$^2$ days 1 and 8 every 21 days) for three cycles | Chemo-naïve Stage IIIb or IV, ECOG PS≤1 | Clin Cancer Res 2004; 10: 5022-6 |
| Fossella 2003 | Docetaxel 75 mg/m$^2$ plus cisplatin 75 mg/m$^2$ (both as 1h iv infusions on day 1, repeated every 3 weeks) | Docetaxel 75 mg/m$^2$ 1h iv plus carboplatin iv AUC 6 mg/mL (both on day 1, repeated every 3 weeks) versus Vinorelbine 25 mg/m$^2$ as a 6- to 10-min iv on days 1, 8, 15, and 22, plus cisplatin 100 mg/m$^2$ iv on day 1, repeated every 4 weeks | Chemo-naïve Stage IIIb or IV, Karnofsky PS≥70% | J Clin Oncol 2003; 21: 3016-24 |
| Gebbia 2003† | Cisplatin 100 mg/m$^2$ iv over 2 h plus Vinorelbine 25 mg/m$^2$ iv bolus on days 1 and 8 | Gemcitabine 1400 mg/m$^2$ given iv over 30 min on days 1 and 8, plus Cisplatin 100 mg/m$^2$ iv over 2h on day 8 | Chemo-naïve Stage IIIb or IV, WHO PS≤2 | Lung Cancer 2003; 39: 179 -89 |
| Gou 2007 | Paclitaxel 135mg/m$^2$ on day 1, Cisplatin 30mg/m$^2$ on days 1-3 | Gemcitaine 1000mg/m$^2$ on days 1 and 8, Cisplatin 30mg/m$^2$ on days 1-3 | Chemo-naïve Stage & PS not reported | Chin J Lung Cancer 2007; 10: 141-3 |

| Study ID | Intervention (with dosage) | Comparators (with dosages) | Population (PS = Performance Status) | Primary study reference (abbreviated) |
|---|---|---|---|---|
| Gridelli 2003 (trial consisted of three treatment arms – only the two relevant arms are presented here) | Gemcitabine1,000 mg/m$^2$ plus vinorelbine 25 mg/m$^2$ on days 1 and 8.<br>Additional therapy was at the discretion of the investigators. Cycles were given every 3 weeks and a total of 6 planned. | Gemcitabine 1,200 mg/m$^2$ on days 1 and 8 plus cisplatin 80 mg/m$^2$ on day 1<br>versus<br>Vinorelbine 30 mg/m$^2$ on days 1 and 8 plus cisplatin 80 mg/m$^2$ on day 1.<br>Cycles were given every 3 weeks and a total of 6 planned | Chemo-naïve<br>Stage IIIb or IV, ECOG PS≤2 | J Clin Oncol 2003; 21:3025-3034 |
| Helbekkmo 2007 | Carboplatin iv over 1h on day 1, and Vinorelbine on days 1 and 8. Carboplatin dose was calculated by the Chatelut formula using AUC¼4, which approximates Calvert AUC¼5. Vinorelbine 25 mgm$^{-2}$ was given as a 10 min iv infusion | Carboplatin iv over 1h was administered on day 1, and Gemcitabine on days 1 and 8. Carboplatin dose was calculated by the Chatelut formula using AUC¼4, which approximates Calvert AUC¼5. Gemcitabine 1000 mgm$^{-2}$ iv for 30 min | Chemo-naïve<br>Stage IIIb or IV, WHO PS≤2 | Brit J Cancer 2007; 97: 283-89 |
| Jiang 2003 | Gemcitabine/Carboplatin<br>At least 2 cycles of 28 days each | Paclitaxel/Carboplatin<br>At least 2 cycles of 28 days each | Chemo-naïve<br>Stage and PS not reported | Chin J Lung Cancer 2003; 6: 135-7 |
| Kelly 2001 | Paclitaxel 225 mg/m2 over 3 h with Carboplatin (AUC 6), day 1 every 21 days with a minimum of 6 cycles | Vinorelbine 25 mg/m$^2$/wk and Cisplatin 100 mg/m$^2$/d, day 1 every 28 days with a minimum of 6 cycles | Chemo-naïve<br>Stage IIIb or IV, PS=0 | J Clin Oncol 2001; 19: 3210-8 |
| Langer 2007 | Paclitaxel 200 mg/m$^2$ iv day 1 over 3h. Carboplatin was administered (AUC 6), over 30 mins immediately after Paclitaxel. Treatment was cycled at 3-week intervals | Gemcitabine 1,000mg/m$^2$ iv over 30 mins on days and 8 and Cisplatin 60 mg/m2 iv day 1 over 1 h. Cycles were repeated every 3 weeks | Chemo-naïve<br>Stage IIIb or IV or recurrent ECOG PS=0 | J Clin Oncol 2007; 25: 418-23 |
| Martoni 2005 | Vinorelbine 25 mg/m$^2$ on days 1 and 8 iv bolus plus Cisplatin 75 mg/m$^2$ on day 1. Cycles lasted three weeks with a maximum of 6 cycles | Gemcitabine 1200 mg/m$^2$ on days 1 and 8 as an iv 30min infusion plus Cisplatin 75 mg/m$^2$ on day 1. Cycles lasted three weeks with a maximum of 6 cycles | Chemo-naïve<br>Stage IIIb or IV, Karnofsky PS≥70% | Eur J Cancer 2005; 41: 81-92 |
| Mazzanti 2003 | Gemcitabine/Carboplatin over a 21 day cycle (Gemcitabine 1200 mg/m$^2$ over 30 min on days 1 and 8); Carboplatin (AUC 5) given over 60 min on day 2) | Gemcitabine/Cisplatin over a 21 day cycle (Gemcitabine 1200 mg/m$^2$ over 30 min on days 1 and 8); Cisplatin 80 mg/m$^2$ over 45 min | Chemo-naïve<br>Stage IIIb or IV, ECOG PS≤2 | Lung Cancer 2003;41: 81-89 |
| Melo 2002 (trial consisted of four treatment arms – only the three relevant arms are presented here) | Cisplatin 100 mg/m$^2$ day 1, vinorelbine 30 mg/m$^2$ day 1, 8, 15 q28d | Cisplatin 100 mg/m$^2$ day 1, gemcitabine 1000 mg/m$^2$ day 1, 8, 15 q28d<br>versus<br>Gemcitabine 1000 mg/m$^2$ day 1, 8, 15, cisplatin 100 mg/m$^2$ day 15 q28d | Locally advanced and metastatic NSCLC | Proc Am Soc Clin Oncol 21: 2002 (abstr 1205) |

| Study ID | Intervention (with dosage) | Comparators (with dosages) | Population (PS = Performance Status) | Primary study reference (abbreviated) |
|---|---|---|---|---|
| Ohe 2007 | Paclitaxel 200 mg/m$^2$ over 3h followed by Carboplatin (AUC 6.0) on day 1 (cycle repeated every 3 weeks for three or more cycles) | Cisplatin 80 mg/m$^2$ of on day 1 and Gemcitabine 1000 mg/m$^2$ of on days 1, 8 (cycle repeated every 3 weeks for three or more cycles) versus Cisplatin 80 mg/m$^2$ on day 1 and Vinorelbine 25 mg/m$^2$ of on days 1, 8 (cycle repeated every 3 weeks for three or more cycles) | Chemo-naïve Stage IIIb or IV, ECOG PS≤1 | Ann Oncol 18: 317–323, 2007 |
| Rosell 2002 | Paclitaxel 200 mg/m2 (3-h intravenous infusion) followed by carboplatin at an AUC of 6, all repeated every 3 weeks | Paclitaxel 200 mg/m2 (3-h intravenous infusion) followed by cisplatin at a dose of 80 mg/m2, all repeated every 3 weeks | Chemo-naïve Stage IIIb or IV, ECOG PS≤2 | Annals of Oncology 13: 1539–1549, 2002 |
| Rubio 2003 | Docetaxel at 75 mg/m2 and carboplatin at 300 mg/m2 (28-day cycles) | Vinorelbine at 17 mg/m2 in days 1 and 14 + Carboplatin at same doses (28-day cycles) | Chemo-naïve Stage IIIb or IV, PS not reported | Proc Am Soc Clin Oncol 22: 2003 (abstr 2827) |
| Scagliotti 2002 | Gemcitabine 1,250 mg/m2 days 1 and 8 plus cisplatin 75 mg/m2 day 2 every 21 days | Paclitaxel 225 mg/m2 (3-hour infusion) then carboplatin (AU the concentration-time curve of 6 mg/mL·min), both on day 1 every 21 days versus Vinorelbine 25 mg/m2/wk for 12 weeks then every other week plus cisplatin 100 mg/m2 day 1 every 28 days | Chemo-naïve Stage IV, ECOG PS≤2 | J Clin Oncol 2002; 20:4285-4291 |
| Schiller 2002 | Paclitaxel 135 mg/m$^2$ administered over 24h on day 1, followed by Cisplatin 75 mgm$^2$ on day 2 (3-week cycles) | Gemcitabine 1000 mg/m$^2$ was administered on days 1, 8, and 15, and Cisplatin 100 mgm$^2$ was administered on day 1 (4-week cycles) versus Docetaxel 75 mg/m$^2$ and Cisplatin 75 mgm$^2$ on day 1 (3-week cycles) versus Paclitaxel 225 mg/m$^2$ given over 3h on day 1, followed on the same day by Carboplatin (AUC 6.0 ), (3-week cycles) | Chemonaïve patients with NSCLC stage IIIB/IV or recurrent disease | N Engl J Med 2002; 346: 92-8 |
| Smit 2003 (earlier published as Van Meerbeck 2001) | Paclitaxel 175 mg/m$^2$ on day 1 followed by Cisplatin 80 mg/m$^2$ on day 1 (3-week cycles) | Gemcitabine 1,250 mg/m$^2$ on days 1 and 8 and Cisplatin 80 mg/m$^2$ on day 1 after Gemcitabine (3-week cycles) | Chemo-naïve Stage IIIb or IV, ECOG PS≤2 | J Clin Oncol 2003; 21: 3909-17 |
| Thomas 2006 (earlier published as Thomas 2002) | Gemcitabine 1250mg/m$^2$ on days 1 and 8 plus Carboplatin (AUC 6) on day 1 (3-week cycles) | Vinorelbine 30mg/m$^2$ weekly plus Cisplatin 80mg/m$^2$ on day 1 (3-week cycles) | Chemo-naïve Stage IIIb or IV, WHO PS≤2 | Lung Cancer 2006; 51: 105-14 |

| Study ID | Intervention (with dosage) | Comparators (with dosages) | Population (PS = Performance Status) | Primary study reference (abbreviated) |
|---|---|---|---|---|
| Treat 2003 | Gemcitabine 1,000 mg/m$^2$ iv on days 1, 8 plus Carboplatin (AUC 5.5) on day 1 (3-week cycles) | Paclitaxel 225 mg/m$^2$ plus Carboplatin (AUC 6.0) on day 1 (3-week cycles) | Chemo-naïve Stage IIIb or IV, ECOG PS≤2 | Proc Am Soc Clin Oncol 22: 2003 (abstr 2511) |
| Tsai 2003 | Vinorelbine 20 mg/m$^2$ on days 1,8,15 plus Cisplatin 80 mg/m$^2$ on day 15) (4-week cycles) | Gemcitabine 1,000 mg/m$^2$ on days 1,8,15 plus Cisplatin 80 mg/m$^2$ on day 15) (4-week cycles) | Chemo-naïve Stage IIIb or IV, PS≤2 | Proc Am Soc Clin Oncol 22: 2003 (abstr 2616) |
| Zatloukal 2003 | Gemcitabine 1200 mg/m$^2$ iv over 30 min on days 1 and 8 plus Cisplatin 80 mg/m$^2$ iv. Platinum analogues were administered at least 4h after Gemcitabine injection on day 1. Two weeks of treatment followed by a week of rest (3-week cycles) | Gemcitabine 1200 mg/m$^2$ iv over 30 min on days 1 and 8 plus carboplatin AUC=5 iv. Platinum analogues were administered at least 4h after gemcitabine injection on day 1. Two weeks of treatment followed by a week of rest (3-week cycles) | Chemo-naïve Stage IIIb or IV, Karnofsky PS≥70% | Lung Cancer 2003; 41: 321-331 |

*trial was a study of doublet chemotherapy followed by taxane therapy – only results from the initial phase are presented
†trial consisted of four treatment arms – only the two relevant arms are presented

## Trial Network

The results of the literature search enabled the construction of a network of connected randomised controlled trials depicted in **Figure 16**. This constitutes the maximum number of comparisons available for any analysis. The actual number included in each individual analysis is reported below and was limited by the reporting of required data within the individual publications.

## Data Analysis

Extracted data from the individual trials has been supplied in section 10.8 **Appendix 8**.

*Overall Survival:* Hazard ratios were only reported by a single trial in the network[52]. Hazard ratios for 11 other trials[6,17,37-39,41,44,45,49,55,56] were obtained from previously conducted meta-analyses[57,58]. Of the 12 trials available, as two were three-armed trials[17,52] and one was a four-armed trial[6], this gave 16 unconstrained data points for analysis.

Unfortunately an estimate of overall survival was unavailable for vinorelbine/carboplatin.

The results for the MTC for overall survival are presented in **Table 8**; these are the results from the fixed effects model as it had a lower DIC than the random effects model (-12.6 vs -11.2, respectively). The fixed effects model would be considered a good fit for the data, as the posterior mean residual deviance was 13.4.

**Table 8.** Hazard ratios (HR) for overall survival calculated from the mixed treatment comparison (fixed effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, intention-to-treat population (HR<1 is better than paclitaxel/carboplatin; HR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 1.2% |
| Paclitaxel/Cisplatin | 0.91 | 0.80 | 1.04 | 33.2% |
| Docetaxel/Carboplatin | 1.03 | 0.80 | 1.32 | 7.0% |
| Docetaxel/Cisplatin | 0.94 | 0.78 | 1.14 | 16.6% |
| Gemcitabine/Carboplatin | 0.95 | 0.73 | 1.23 | 26.6% |
| Gemcitabine/Cisplatin | 0.92 | 0.81 | 1.04 | 15.3% |
| Vinorelbine/ Carboplatin | ND | ND | ND | ND |
| Vinorelbine/Cisplatin | 1.08 | 0.90 | 1.28 | 0.0% |

ND = No Data

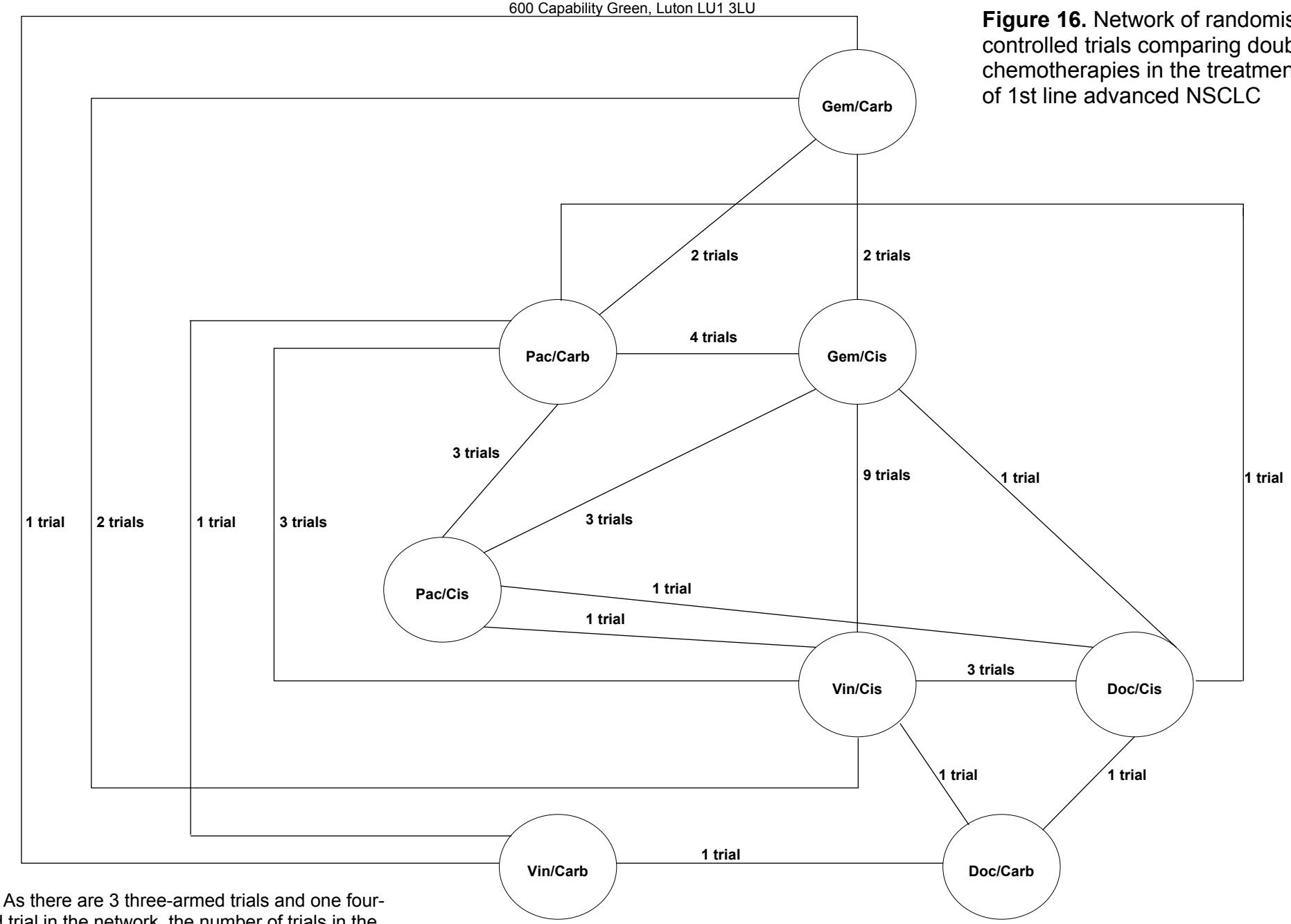



**Figure 16.** Network of randomised controlled trials comparing doublet chemotherapies in the treatment of 1st line advanced NSCLC

**Note:** As there are 3 three-armed trials and one four-armed trial in the network, the number of trials in the figure sums to 39 rather than 28.

*Progression-Free Survival:* Hazard ratios for progression-free survival were unavailable from any of the identified trials. However, the two previously mentioned meta-analyses[57,58] were able to supply these data for six trials in the network[6,17,33,41,45,59]. Of the six trials available, as one was three-armed[17] and one was a four-armed trial[6], this gave nine unconstrained data points for analysis.

Unfortunately an estimate of progression-free survival was unavailable for docetaxel/carboplatin or vinorelbine/carboplatin.

The results for the MTC for progression-free survival are presented in **Table 9**; these are the results from the fixed effects model as it had a lower DIC than the random effects model (-6.6 vs -5.1, respectively). The fixed effects model would be considered a good fit for the data, as the posterior mean residual deviance was 8.0.

**Table 9.** Hazard ratios (HR) for progression-free survival calculated from the mixed treatment comparison (fixed effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, intention-to-treat population (HR<1 is better than paclitaxel/carboplatin; HR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 8.1% |
| Paclitaxel/Cisplatin | 1.14 | 0.93 | 1.38 | 0.3% |
| Docetaxel/Carboplatin | ND | ND | ND | ND |
| Docetaxel/Cisplatin | 1.06 | 0.85 | 1.31 | 4.6% |
| Gemcitabine/Carboplatin | 1.23 | 0.68 | 2.06 | 16.6% |
| Gemcitabine/Cisplatin | 0.92 | 0.81 | 1.05 | 56.3% |
| Vinorelbine/Carboplatin | ND | ND | ND | ND |
| Vinorelbine/Cisplatin | 0.99 | 0.80 | 1.21 | 14.2% |

ND = No Data

*Objective Response:* Data on objective response were available from 24 trials[5-7,17,18,34-37,39-44,46-54]. As this includes four three-armed trials[7,17,39,52] and one four-armed trial[6], the number of unconstrained data points was 53.

The results for the MTC for objective response are presented in **Table 10**; these are the results from the fixed effects model as it had a lower DIC than the random effects model (339.7 vs 340.3, respectively). The fixed effects model would be considered a good fit for the data, as the posterior mean residual deviance was 49.9.

**Table 10.** Odds ratios (OR) for objective response calculated from the mixed treatment comparison (fixed effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, intention-to-treat population (OR>1 is better than paclitaxel/carboplatin; OR<1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 0.2% |
| Paclitaxel/Cisplatin | 1.16 | 0.93 | 1.44 | 16.2% |
| Docetaxel/Carboplatin | 0.95 | 0.67 | 1.32 | 0.8% |
| Docetaxel/Cisplatin | 1.26 | 0.97 | 1.61 | 40.5% |
| Gemcitabine/Carboplatin | 0.85 | 0.65 | 1.09 | 0.1% |
| Gemcitabine/Cisplatin | 1.15 | 0.94 | 1.41 | 11.1% |
| Vinorelbine/Carboplatin | 1.12 | 0.33 | 2.84 | 29.3% |
| Vinorelbine/Cisplatin | 1.09 | 0.90 | 1.32 | 1.9% |

*Anaemia:* Data on anaemia were available from 20 trials[5-7,17,18,33-37,39,41,44,46-50,52,53]. As this includes three three-armed trials[7,17,52] and one four-armed trial[6], the number of unconstrained data points was 45.

The results for the MTC for anaemia are presented in **Table 11**; these are the results from the random effects model as it had a lower DIC than the fixed effects model (272.4 vs 276.7, respectively). The random effects model would be considered a reasonable fit for the data, as the posterior mean residual deviance was 49.9.

**Table 11.** Odds ratios (OR) for anaemia calculated from the mixed treatment comparison (random effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, safety population (OR<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 28.1% |
| Paclitaxel/Cisplatin | 1.11 | 0.64 | 1.81 | 20.7% |
| Docetaxel/Carboplatin | 1.42 | 0.57 | 3.19 | 14.0% |
| Docetaxel/Cisplatin | 1.17 | 0.66 | 2.09 | 16.2% |
| Gemcitabine/Carboplatin | 6.10 | 2.65 | 12.61 | 0.0% |
| Gemcitabine/Cisplatin | 2.71 | 1.75 | 3.98 | 0.0% |
| Vinorelbine/Carboplatin | 1.75 | 0.40 | 5.03 | 21.0% |
| Vinorelbine/Cisplatin | 2.77 | 1.76 | 4.15 | 0.0% |

ND = No Data

*Diarrhoea:* Data on diarrhoea were available from nine trials[6,7,39,40,46,48-50,52]. As this includes three three-armed trials[7,39,52] and one four-armed trial[6], the number of unconstrained data points was 22. Gemcitabine/carboplatin could not be included in the analysis as there were zero events associated with it in the three trials that reported this outcome (two vs gemcitabine/cisplatin[37,44] and one vs vinorelbine/cisplatin[42]).

The results for the MTC for diarrhoea are presented in **Table 12**; these are the results from the fixed effects model, as it had a lower DIC than the random effects model (110.4 vs 110.7, respectively). The fixed effects model would be

considered a good fit for the data, as the posterior mean residual deviance was 22.3.

**Table 12.** Odds ratios (OR) for diarrhoea calculated from the mixed treatment comparison (fixed effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, safety population (OR<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 5.7% |
| Paclitaxel/Cisplatin | 2.46 | 1.20 | 4.63 | 0.0% |
| Docetaxel/Carboplatin | 3.24 | 1.25 | 7.07 | 0.0% |
| Docetaxel/Cisplatin | 4.37 | 2.20 | 8.30 | 0.0% |
| Gemcitabine/Carboplatin | ND | ND | ND | ND |
| Gemcitabine/Cisplatin | 1.13 | 0.48 | 2.27 | 5.2% |
| Vinorelbine/Carboplatin | 0.41 | 0.01 | 1.98 | 87.8% |
| Vinorelbine/Cisplatin | 1.36 | 0.57 | 2.80 | 1.4% |

ND = No Data

*Fatigue:* Data on fatigue were available from 6 trials[5,7,35,39,47,49]. As this includes one three-armed trial[7] the number of unconstrained data points was 13. No data were available from the trials evaluating vinorelbine/carboplatin[33,40], docetaxel/carboplatin[40], or gemcitabine/carboplatin[18,33-35,37,44,51]. Docetaxel/cisplatin could not be included as the single trial[48] comparing it with vinorelbine/cisplatin had zero events in both treatment arms.

The results for the MTC for fatigue are presented in **Table 13**; these are the results from the fixed effects model as it had a lower DIC than the random effects model (74.2 vs 74.7, respectively). The fixed effects model would be considered a good fit for the data, as the posterior mean residual deviance was 15.0.

**Table 13.** Odds ratios (OR) for fatigue calculated from the mixed treatment comparison (fixed effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, safety population (OR<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 57.3% |
| Paclitaxel/Cisplatin | 1.22 | 0.72 | 1.97 | 21.6% |
| Docetaxel/Carboplatin | ND | ND | ND | ND |
| Docetaxel/Cisplatin | ND | ND | ND | ND |
| Gemcitabine/Carboplatin | ND | ND | ND | ND |
| Gemcitabine/Cisplatin | 1.46 | 0.68 | 2.81 | 16.7% |
| Vinorelbine/Carboplatin | ND | ND | ND | ND |
| Vinorelbine/Cisplatin | 1.58 | 0.86 | 2.66 | 4.4% |

ND = No Data

*Febrile Neutropenia:* Data on febrile neutropenia were available from 13 trials[5-7,17,18,35,39,42,46,48,50,52]. As this includes three three-armed trials[7,17,52] and one four-armed trial[6], the number of unconstrained data points was 31. Vinorelbine/carboplatin could not be included in the analysis as there were zero events associated with it in the single trial that reported this outcome[40].

The results for the MTC for febrile neutropenia are presented in **Table 14**; these are the results from the random effects model as it had a lower DIC than the fixed effects model (162.7 vs 189.9, respectively). The random effects model would be considered a good fit for the data, as the posterior mean residual deviance was 31.2.

**Table 14.** Odds ratios (OR) for febrile neutropenia calculated from the mixed treatment comparison (random effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, safety population (OR<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 0.1% |
| Paclitaxel/Cisplatin | 0.99 | 0.29 | 2.42 | 0.9% |
| Docetaxel/Carboplatin | 1.67 | 0.19 | 6.64 | 2.4% |
| Docetaxel/Cisplatin | 1.36 | 0.39 | 3.61 | 0.1% |
| Gemcitabine/Carboplatin | 0.25 | 0.02 | 1.01 | 74.0% |
| Gemcitabine/Cisplatin | 0.39 | 0.12 | 0.96 | 22.5% |
| Vinorelbine/Carboplatin | ND | ND | ND | ND |
| Vinorelbine/Cisplatin | 1.97 | 0.70 | 4.57 | 0.0% |

ND = No Data

*Nausea and Vomiting:* Data on nausea and vomiting were available from 19 trials[5-7,17,34-37,39,41,42,44,46-50,52,53].As this includes three three-armed trials[7,17,52] and one four-armed trial,[6] the number of unconstrained data points was 43. However, nausea and vomiting were only reported as a combined outcome in six trials[34-37,42,44]. For the 13 other trials, the individually reported adverse events of nausea and vomiting were combined. This may have inadvertently double counted some events (i.e. when the same patient had nausea and vomiting). No data were available from the trials evaluating vinorelbine/carboplatin[33,40].

The results for the MTC for nausea and vomiting are presented in **Table 15**; these are the results from the random effects model as it had a lower DIC than the fixed effects model (259.2 vs 313.2, respectively). The random effects model would be considered a good fit for the data, as the posterior mean residual deviance was 42.4.

**Table 15.** Odds ratios (OR) for nausea and vomiting calculated from the mixed treatment comparison (random effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, safety population (OR<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 65.8% |
| Paclitaxel/Cisplatin | 4.01 | 1.39 | 9.51 | 0.3% |
| Docetaxel/Carboplatin | 3.76 | 0.48 | 14.57 | 10.3% |
| Docetaxel/Cisplatin | 5.86 | 1.79 | 15.50 | 0.0% |
| Gemcitabine/Carboplatin | 1.60 | 0.43 | 3.97 | 23.7% |
| Gemcitabine/Cisplatin | 5.44 | 2.34 | 10.85 | 0.0% |
| Vinorelbine/Carboplatin | ND | ND | ND | ND |
| Vinorelbine/Cisplatin | 4.16 | 1.77 | 8.46 | 0.0% |

ND = No Data

*Neutropenia:* Data on neutropenia were available from 18 trials[5-7,17,18,34-37,39,41,42,46,48-50,52,53]. As this includes three three-armed trials[7,17,52] and one four-armed trial[6], the number of unconstrained data points was 41. No data were available from the trials evaluating vinorelbine/carboplatin[33,40].

The results for the MTC for neutropenia are presented in **Table 16**; these are the results from the random effects model as it had a lower DIC than the fixed effects model (281.5 vs 342.5, respectively). The random effects model would be considered a good fit for the data, as the posterior mean residual deviance was 41.3.

**Table 16.** Odds ratios (OR) for neutropenia calculated from the mixed treatment comparison (random effects model) in the 1st-line treatment of advanced non-small-cell lung cancer, safety population (OR<1 is better than paclitaxel/carboplatin; OR>1 is worse than paclitaxel/carboplatin)

| Treatment | Mean | 95% Credible Interval | | Probability "best" |
|---|---|---|---|---|
| | | Lower | Upper | |
| Paclitaxel/Carboplatin | 1.00 | -- baseline treatment -- | | 1.4% |
| Paclitaxel/Cisplatin | 0.76 | 0.30 | 1.52 | 29.9% |
| Docetaxel/Carboplatin | 1.81 | 0.31 | 6.09 | 8.4% |
| Docetaxel/Cisplatin | 1.29 | 0.47 | 2.92 | 2.6% |
| Gemcitabine/Carboplatin | 0.85 | 0.29 | 1.94 | 27.9% |
| Gemcitabine/Cisplatin | 0.70 | 0.36 | 1.24 | 29.8% |
| Vinorelbine/Carboplatin | ND | ND | ND | ND |
| Vinorelbine/Cisplatin | 2.24 | 1.14 | 4.02 | 0.0% |

### Heterogeneity

Hetergeneity was found to be moderate/low in all analyses where it was assessed (tau≤ 0.79), i.e. for those outcomes where a random effects model was deemed to be more appropriate than a fixed effects model.

### COMMENT

No individual doublet chemotherapy was identified as offering substantial clinical benefit, over the other doublet chemotherapies assessed, in addition to the most favourable tolerability profile. There were no statistically significant

differences (at the 5% level) identified compared to paclitaxel/carboplatin for any of the efficacy outcomes (overall survival, progression-free survival and objective response). Similarly no alternative doublet chemotherapy demonstrated a statistically significant reduction in risk of any of the adverse events assessed compared to paclitaxel/carboplatin, with the exception of gemcitabine/cisplatin that has less risk of febrile neutropenia (OR 0.39, 95% CI: 0.12 to 0.96). However, some statistically significant increases in risk of an adverse event compared to paclitaxel/carboplatin were identified. These are:

- Gemcitabine-based chemotherapies and vinorelbine/cisplatin significantly increase the risk of anaemia compared to paclitaxel/carboplatin;

- Paclitaxel/cisplatin and docetaxel-based chemotherapies significantly increase the risk of diarrhoea;

- All cisplatin-based chemotherapies significantly increase the risk of nausea and vomiting;

- Vinorelbine/cisplatin significantly increases the risk of neutropenia.

Overall, vinorelbine/cisplatin would appear to have the least favourable adverse event profile, of the doublet chemotherapies assessed, compared to paclitaxel/carboplatin.

## *6.7 Safety in IPASS study population*

**Safety and Tolerability in IPASS (EFS Population)**

In IPASS, the differences in toxicity profiles between gefitinib and doublet chemotherapy are mainly due to the differences in the mode of action of the two treatment regimes. Gefitinib is a targeted therapy acting on the EGFR-TK pathway and it is not generally associated with the cytotoxic side effects commonly seen with chemotherapy. This in turn has a significant impact on the patient's health-related quality of life (as described above in section 6.4).

Fewer patients in the gefitinib arm were hospitalised because of haematological AEs (4 patients [0.7%] in the gefitinib arm and 18 [3.1%] in the paclitaxel/carboplatin arm). For 3 of the 4 patients in the gefitinib arm, the hospitalisations occurred after discontinuation of gefitinib treatment and whilst receiving second-line paclitaxel/carboplatin treatment. This data included hospitalisations which occurred with in 28 days of the last dose.

The most common adverse events are reported in Table 17. Gefitinib was associated with fewer CTC grade 3/4 adverse events (28.7% versus 61.0%), fewer dose modifications due to toxicity (16.1% versus 35.2% for carboplatin and 37.5% for paclitaxel), and fewer adverse events leading to discontinuation (6.9% versus 13.6%) than paclitaxel/carboplatin. Adverse events leading to death and serious adverse events leading to hospitalisation occurred in 3.8% and 2.7%, and 13.8% and 13.1% of gefitinib and paclitaxel/carboplatin patients, respectively.

## Table 17: Common Adverse Events

Events are included if they occurred in at least 10% of patients in either treatment group, either while the patients were receiving treatment or during the 28 day follow-up, and if there was at least a 5% difference between groups

| Adverse Events | Gefitinib (n=607) | | Paclitaxel/carboplatin (n=589) | |
|---|---|---|---|---|
| | All adverse events | CTC Grade 3/4/5 | All adverse events | CTC Grade 3/4/5 |
| Rash/acne[a] | 402 (66.2) | 19 (3.1) | 132 (22.4) | 5 (0.8) |
| Diarrhoea | 283 (46.6) | 23 (3.8) | 128 (21.7) | 8 (1.4) |
| Dry skin | 145 (23.9) | 0 (0) | 17 (2.9) | 0 (0) |
| Anorexia[a] | 133 (21.9) | 9 (1.5) | 251 (42.6) | 16 (2.7) |
| Pruritus[a] | 118 (19.4) | 4 (0.7) | 74 (12.6) | 1 (0.2) |
| Stomatitis[a] | 103 (17.0) | 1 (0.2) | 51 (8.7) | 1 (0.2) |
| Asthenic conditions[a] | 102 (16.8) | 2 (0.3) | 259 (44.0) | 11 (1.9) |
| Nausea[a] | 101 (16.6) | 2 (0.3) | 261 (44.3) | 9 (1.5) |
| Paronychia | 82 (13.5) | 2 (0.3) | 0 (0) | 0 (0) |
| Vomiting | 78 (12.9) | 1 (0.2) | 196 (33.3) | 16 (2.7) |
| Constipation | 73 (12.0) | 0 (0) | 173 (29.4) | 1 (0.2) |
| Alopecia | 67 (11.0) | 0 (0) | 344 (58.4) | 0 (0) |
| Neurotoxicity[a] | 66 (10.9) | 2 (0.3) | 412 (69.9) | 29 (4.9) |
| Myalgia | 47 (7.7) | 3 (0.5) | 186 (31.6) | 10 (1.7) |
| Arthralgia | 39 (6.4) | 1 (0.2) | 113 (19.2) | 6 (1.0) |
| Neutropenia (Any)[b] | - | 22 (3.7) | - | 387 (67.1) |
| Febrile neutropenia | 1 (0.2) | 1 (0.2) | 17 (2.9) | 17 (2.9) |
| Anaemia[b] | - | 13 (2.2) | - | 61 (10.6) |
| Leucopenia[b] | - | 9 (1.5) | - | 202 (35.0) |

Data are numbers (%) of patients. Events while on randomised treatment or during the 28-day follow-up.

[a]Grouped term (sum of high-level and preferred terms)

[b]Data from laboratory reports. Worsening in laboratory value (absolute neutrophil count for neutropenia, hemoglobin for anaemia, and white blood cell count for leucopenia) from baseline to CTC grade 3-4. n=599 with gefitinib and 577 with paclitaxel/carboplatin.

CTC, Common Terminology Criteria

The incidences of rash/acne, diarrhoea and elevated liver transaminases were significantly higher with gefitinib than with paclitaxel/carboplatin, while the incidences of neurotoxicity, nausea, vomiting and haematologic toxicity (neutropenia, febrile neutropenia, anaemia and leucopenia) were significantly higher with paclitaxel/carboplatin (Table 18).

Interstitial lung disease (ILD)-type events occurred in 16 (2.6%) and 8 (1.4%) of gefitinib and paclitaxel/carboplatin patients, and led to three and one deaths, respectively. It is known that ILD occur more frequently in the Asian population than in a Caucasian population on gefitinib therapy. Indeed, the rates of ILD reported in the large phase III INTEREST and ISEL studies (conducted in predominantly Caucasian patients) were 1% in both the gefitinib and control arms (docetaxel and placebo respectively)[13,14].

**Table 18: Analysis of Specific Safety Events (Evaluable-for-Safety Population)[a]**

| | Number (%) of Patients | | |
|---|---|---|---|
| **Event[b]** | **Gefitinib (n=607)** | **Paclitaxel/carboplatin (n=589)** | **Adjusted P-value[c]** |
| **Rash/acne[d]** | 398 (65.6) | 132 (22.4) | <0.0001 |
| **Diarrhoea** | 274 (45.1) | 128 (21.7) | <0.0001 |
| **Nausea** | 74 (12.2) | 260 (44.1) | <0.0001 |
| **Vomiting** | 59 (9.7) | 193 (32.8) | <0.0001 |
| **Elevated Liver Transaminases (CTC ≥ Grade 3)[e]** | 57 (9.4) | 6 (1.0) | <0.0001 |
| **Neurotoxicity[d]** | 30 (4.9) | 411 (69.8) | <0.0001 |
| **Neutropenia (CTC > Grade 3)[e]** | 4 (0.7) | 385 (65.4) | <0.0001 |
| **Leucopenia (CTC > Grade 3)[e]** | 1 (0.2) | 202 (34.3) | <0.0001 |
| **Anaemia (CTC > Grade 3)[e]** | 11 (1.8) | 56 (9.5) | <0.0001 |
| **Thrombocytopenia (CTC > Grade 3)[e]** | 5 (0.8) | 29 (4.9) | 0.0001 |

[a]Specified events anticipated to be more common with gefitinib: rash/acne, diarrhoea, nausea, vomiting, elevated liver transaminases. Specified events anticipated to be more common with paclitaxel/carboplatin: neurotoxicity, neutropenia, leucopenia, anaemia, thrombocytopenia.

[b]Data derived from adverse events and laboratory data reported on-treatment.

[c]Calculated using the method of Westfall and Young.

[d]Grouped term (sum of high-level and preferred terms).

[e]Worsening in laboratory value (ALT or AST for liver transaminases, absolute neutrophil count for neutropenia, white blood cell count for leucopenia, hemoglobin for anaemia, and platelets for thrombocytopenia) from baseline to CTC grade 3-4.

CTC, Common Terminology Criteria; ALT, alanine transaminase; AST, aspartate aminotransferase.

## Safety and Tolerability in EGFR-TK M+ and EGFR-TK M- populations

### EGFR-TK M+

Overall, for gefitinib-treated patients with an EGFR-TK M+ status, the profile of the most common AEs was similar to that reported in the overall population and consistent with the known safety profile of gefitinib. Some events were reported more frequently but this was generally true across both treatment arms and could therefore be a result of small numbers in comparison to the overall study population rather than a true difference. In addition, some gefitinib specific events, such as rash were reported at a higher incidence in only the gefitinib arm, which may reflect the longer time on treatment in this subgroup compared with the overall population (8.3 versus 5.6 months).

### EGFR-TK M-

The most common AEs reported by gefitinib-treated patients with an EGFR-TK M- status were similar to the overall population and consistent with the known safety profile of gefitinib. However, in contrast with the overall population, lower incidences of some gefitinib-associated events such as dry eye, diarrhea, and pruritus were reported (although most were still reported more commonly with gefitinib than paclitaxel/carboplatin). This may reflect the shorter time on treatment in this subgroup compared with the overall population (1.6 versus 5.6 months. Some events that are also associated with the underlying disease (eg, anorexia and fatigue) were reported at an increased incidence in the gefitinib arm compared with the overall population. This may be because these patients have a shorter time to progression and therefore may have a deterioration of their underlying condition.

Overall, the safety profile of gefitinib by EGFR-TK mutation status was consistent with the overall population with differences likely due to the underlying state of the disease and the length of time on treatment.

**EGFR-TK M Unknown**

The safety profile of the gefitinib-treated patients with an EGFR-TK mutation unknown status was similar to the overall population and consistent with the known safety profile of gefitinib.

The favorable safety profile of gefitinib demonstrated in the phase III studies is consistent with that observed in everyday settings. In addition to the data from clinical trials, the Early Access Program for gefitinib in Caucasian patients indicated that gefitinib is well tolerated by patients with advanced or metastatic NSCLC. The majority of ADRs associated with gefitinib are mild in nature and those most commonly reported are grade 1/2 diarrhoea and skin reactions [60].

Pharmacodynamic differences between gefitinib and cytotoxic chemotherapies may account for gefitinib's favorable tolerability. Traditional chemotherapies are used at their MTD to exert their maximum efficacy but at the cost of a high level of toxicity and poor tolerability. In contrast, gefitinib is used at an optimum biological dose (250 mg o.d) that provides maximum clinical benefit while retaining favorable tolerability.

**Concomitant Medications**

The concomitant treatments administered in IPASS were representative of those commonly prescribed for patients with advanced NSCLC, the expected toxicities for gefitinib and paclitaxel/carboplatin, and co-morbidities commonly seen in patients with advanced NSCLC. A wide variety of concomitant treatments were taken throughout the study by EGFR-TK M+ patients in both treatment groups. More gefitinib-treated EGFR-TK M+ patients received different types of topical corticosteroids to mainly treat skin toxicity events. As required by the protocol, paclitaxel/carboplatin patients received premedication with dexamethasone, diphenhydramine, H2-blockers, and 5-HT3 antagonists. In addition, more paclitaxel/carboplatin EGFR-TK M+ patients received propulsives (59.7% vs 22.7%), benzodiazepine derivates (38.8% vs 27.3%) and contact laxatives (34.1% vs 18.9%). Importantly, 21.7% of patients in the paclitaxel/carboplatin EGFR-TK M+ arm received colony-stimulating factors whilst no patients in the gefitinib EGFR-TK M+ arm

received colony-stimulating factors further highlighting the difference in the toxicity profiles of the two treatment regimes used in IPASS. Granulocyte colony-stimulating factor [filgrastrim] was allowed for prophylaxis of neutropenia (if observed in a previous cycle).

## *6.8 Non-RCT evidence*

None identified

## *6.9 Interpretation of clinical evidence*

### 6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Platinum-based doublet chemotherapy has become established as the standard first-line treatment for advanced NSCLC patients in the UK and no targeted agent (as monotherapy) has demonstrated superiority in efficacy to the current standard of care, doublet chemotherapy.

IPASS establishes that gefitinib, an oral molecular targeted agent, is superior to doublet chemotherapy, an intravenous cytotoxic regimen, as first line treatment for advanced NSCLC patients harbouring activating mutations of the EGFR-TK. Gefitinib also has a more favourable tolerability profile and is associated with improved HRQoL and symptom control compared with doublet chemotherapy in this population.

Progression-free survival was chosen as the primary end-point for IPASS to ensure the efficacy of gefitinib in the first line setting could be assessed without any subsequent therapies influencing the patient's overall survival, completely independent of the effect of gefitinib.

The clinical management of advanced NSCLC remains challenging, but a targeted oral agent that has superior efficacy, a more favourable tolerability profile, and results in better HRQoL and improvement in disease symptoms than intravenous chemotherapy is an important shift in the treatment paradigm for NSCLC and offers an additional superior option for selected patients. Based on this data, gefitinib is a valid treatment option for patients with chemotherapy naïve advanced NSCLC harbouring activating mutations in the EGFR-TK.

### 6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The patient population in IPASS was a clinically selected group of Asian patients being ex-light or never smokers, having adenocarcinoma and chemotherapy naïve resulting in more female patients being recruited in the study than otherwise typical for a general patient population with NSCLC. These clinical characteristics are associated with a higher incidence of EGFR mutations (see Appendix 1: IRESSA SmPC table 6) and this resulted in a population that was enriched for this important biological marker. From planned subgroup analysis, IPASS showed that EGFR mutation status was driving the benefit. Furthermore, Kobayashi and colleagues did not select the study population based on clinical characteristics but rather included EGFR M+ status as inclusion criteria. The study population thus included patients that were adenocarcinoma, large cell carcinoma, adenosquamous carcinoma, squamous carcinoma and those of other histologies. As has been described earlier the outcomes of IPASS and the Kobayashi study in EGFR M+ patients were highly comparable favouring gefitinib over doublet chemotherapy. The results are therefore relevant to the NSCLC patient population with EGFR-TK M+ tumour in UK.

AstraZeneca is working with the NHS to ensure equity of access to the EGFR-TK mutation test to ensure that all advanced NSCLC patients, whose EGFR-TK mutation status is unknown, can be tested for the mutation (see section 5.1 for further detail).

IPASS was conducted using standard doses and administration of chemotherapy and gefitinib as specified in the UK SmPC.

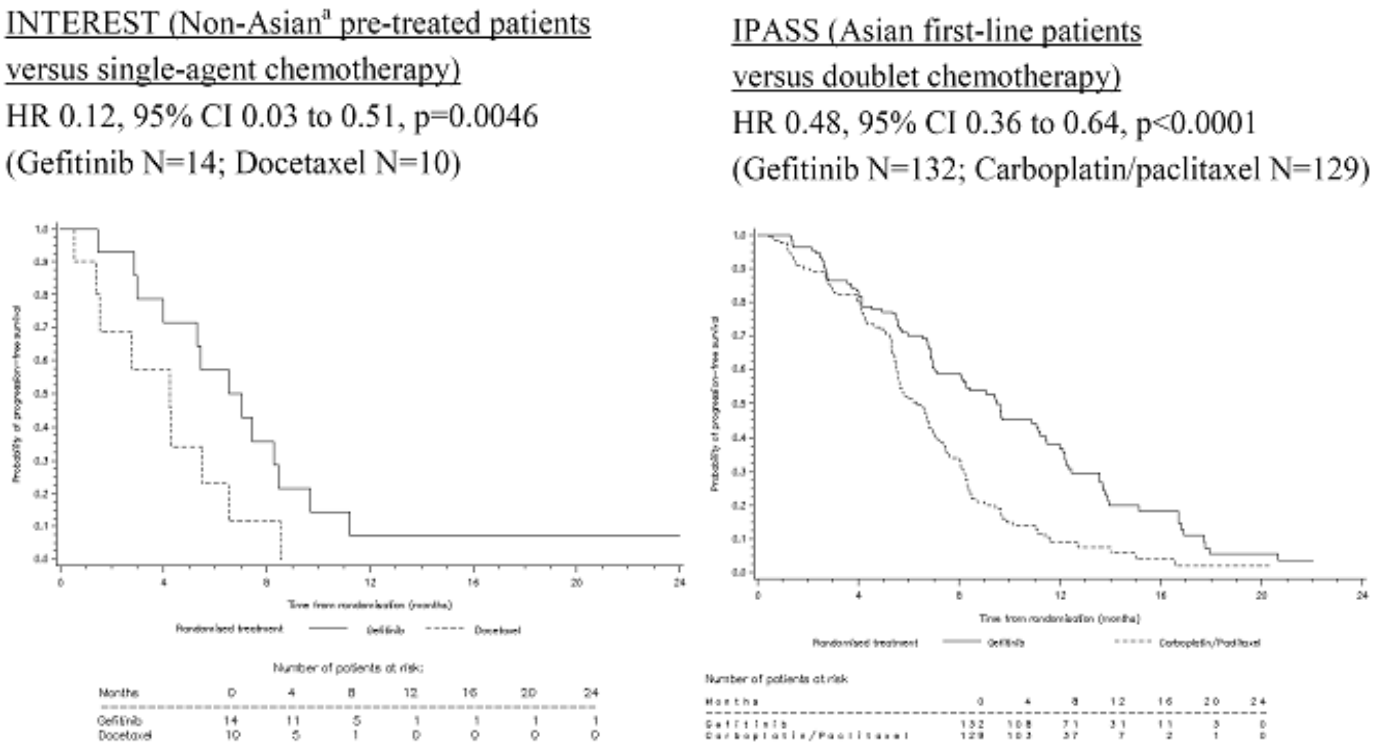
IPASS compared gefitinib (an oral tablet) with doublet chemotherapy (iv infusion), the current standard of care in this setting in the UK. Although the doublet chemotherapy regimen employed in IPASS was paclitaxel/carboplatin, many studies have demonstrated little difference between a variety of doublet chemotherapy regimens including gemcitabine/carboplatin (the predominant regimen used in the UK for the first line treatment of advanced NSCLC) [6,17-19]. This conclusion has also been verified by the mixed-treatment comparison in section 6.6. Many of these studies were conducted in predominantly Caucasian populations typically representative of EGFR M+ patients with advanced NSCLC in the UK.

The efficacy benefits for gefitinib compared to doublet chemotherapy observed in IPASS are supported by other studies which have demonstrated that gefitinib has consistently demonstrated high anti-tumour activity in EGFR-TK M+ patients across studies in all ethnicities and lines of therapy – in EGFR-TK M+ patients, PFS and ORR with gefitinib are significantly greater than both doublet chemotherapy in first-line patients from Asia (IPASS)[9], and singlet chemotherapy in pre-treated non-Asian patients (INTEREST)[14].

For EGFR-TK M+ patients, improved response rates and time to treatment failure were observed for gefitinib compared with placebo in ISEL, significant advantages in PFS and ORR were demonstrated for gefitinib compared to doublet chemotherapy in IPASS, significant advantages in PFS and ORR were shown for gefitinib compared to docetaxel in INTEREST (Figures 11 and 17), and trends for greater PFS and ORR for gefitinib compared to docetaxel in V-15-32 [9,13,14,61].

Furthermore, several prospective single arm studies in EGFR M+ patients conducted in non-Asian countries have consistently demonstrated high response rates and progression free times, supporting the results of the phase III comparative studies and further demonstrating that the positive outcomes observed following gefitinib treatment in EGFR M+ patients is consistent in both Asian and non-Asian patients[62-64].

**Figure 17: Progression-free survival probability for EGFR-TK M+ patients: INTEREST and IPASS**




a Ethnicities included in INTEREST Non-Asian Group: 20 Caucasian, 3 Black, 1 other

Note that within the EGFR M+ subgroups of both INTEREST and IPASS key demographic and baseline characteristics were well balanced across the two treatment groups, therefore the treatment effect is not driven by differences in demographic characteristics.

In pre-treated EGFR-TK M+ patients in the INTEREST study, gefitinib was superior to docetaxel in terms of PFS (HR 0.16, 95% CI 0.05 to 0.49, p=0.0012) and ORR (42.1% versus 21.1%, p=0.0361).

For gefitinib-treated patients, consistent with other studies, ORR, PFS, and overall survival appeared greater for EGFR-TK M+ patients than for EGFR-TK M- patients. The same pattern was observed to a lesser extent for docetaxel-treated patients.

Based on the evidence from Phase III studies it can be concluded that EGFR-TK mutation status is a strong predictive biomarker for differential efficacy benefit with gefitinib.

In conclusion, the benefits of treatment with IRESSA outweigh the risks for patients with advanced NSCLC who are EGFR-TK M+, and the benefit: risk profile for IRESSA is therefore favourable in this population. Therefore, it is considered reasonable that where a positive EGFR-TK mutation test is available the results should be used to inform treatment choice in all lines of therapy

It is proposed that the recommended course of treatment with Gefitinib is 250mg once daily orally until disease progression. This recommended dose has resulted from extensive findings from phase II and phase III studies[9,14,16].

It is suggested that oral gefitinib be made available to NHS patients for the first line treatment of their locally advanced or metastatic NSCLC with EGFR-TK mutations. Gefitinib offers an alternative to the current standard of care, doublet chemotherapy demonstrating superior efficacy benefits (PFS and ORR), greater improvements in health-related quality of life compared to doublet chemotherapy and better tolerability compared to a doublet chemotherapy regimen.

# 7 Cost effectiveness

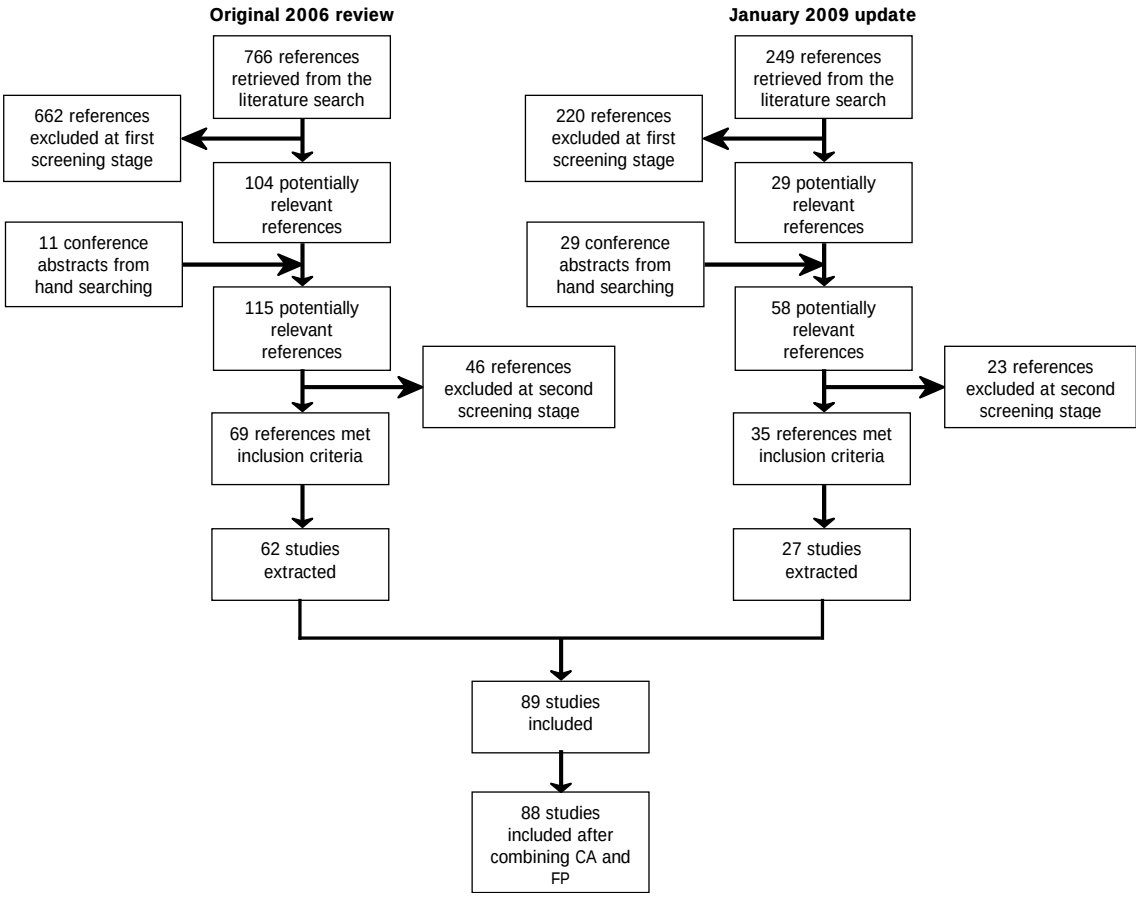
## *7.1 Published cost-effectiveness evaluations*

### 7.1.1 Identification of studies

A systematic review of literature[65], originally carried out in October 2006, was updated in January 2009 to identify cost-effectiveness analyses (CEA) for the 1st line treatment of aNSCLC (see figure 18). Data sources for the review consist of a number of literature databases, conference proceedings and health technology assessments. The following databases were searched: Medline and Medline in Process, Embase, NHS EED/Cochrane Economic Evaluations database and CINAHL, with no date restrictions applied. Full details of the search strategy are provided in Appendix 3.

**Figure 18: Study flow diagram[1]**

[1] CA = conference abstract, FP = full paper




Conference proceedings and journals that were searched by hand were ASCO (2005-2008), ECCO (2005, 2007), World Conference on Lung Cancer (2005, 2007), AACR (2005-2008), ESMO (2005-2008), EORTC-NCI-AACR (2006, 2008) and ISPOR (2005-2008).

HTA reports searched by hand up to April 2009 were sourced from the internet sites for NICE (England and Wales), PBAC (Australia), CCOHTA (Canada), PBB (Sweden) and the SMC (Scotland).

Economic evaluations of patients with stage IIIb/IV non-small cell lung cancer who are treated with treatments currently used in clinical practice for this indication were included.

Studies which enrolled patients with stage IIIa or earlier disease were only included if the majority of patients were at stage IIIb or later, or if a subgroup analysis was performed per disease stage. In addition, studies that did not report the stage of the disease were included.

A total of 88 studies were found which fitted the inclusion criteria. There were 34 studies reported only as conference abstracts (CA) and 54 studies reported as full papers (FP).

Only four[66-69] of the 88 studies identified in the systematic review were considered to be of potential relevance to the decision problem outlined in the NICE scope for this submission. Full texts of these papers were ordered for detailed review.

The remaining studies were excluded for one or more of the following reasons:

- The line of therapy for aNSCLC that was studied was not consistent with the decision problem (i.e. the studies were evaluating 2nd line treatments for aNSCLC)

- The analytical approach was not consistent with the NICE reference case (i.e. the studies reported cost-minimisation analyses (CMA) and/or cost-consequence analyses)

- The cost-effectiveness analyses were not considered generalisable to the UK.

In addition, the reviewers subsequently identified an HTA report of pemetrexed plus cisplatin as a 1st line treatment of aNSCLC[70] that was also included in evidence base.

It should be noted that no studies have been found that have evaluated the cost-effectiveness of gefitinib as a 1st line treatment for aNSCLC.

### 7.1.2 Description of identified studies

| **Study** | **Neymark (2005)[66] Economic evaluation of three two-drug chemotherapy regimens in advanced non-small-cell lung cancer** |
|---|---|
| Aims | Cost-effectiveness analysis of cisplatin plus paclitaxel, gemcitabine plus cisplatin and gemcitabine plus paclitaxel for the treatment of aNSCLC. |
| Methods | Mean overall survival, resource use and associated costs were sourced from a phase III trial that compared the three doublet chemotherapy regimens. The perspective taken was the Dutch health insurance system and tariffs valid for 2002 were applied. The main outcome measure adopted by the researchers was the mean incremental cost per life year saved. Sensitivity analysis was performed by bootstrap techniques and the final results were presented using cost-effectiveness acceptability curves (CEACs). |
| Results | The estimated mean survival times were comparable in the two cisplatin-based regimens (11.3 months vs. 11.8 months mean OS for cisplatin-paclitaxel versus and cisplatin-gemcitabine, respectively) with largely overlapping confidence intervals. There was a 99% probability that cisplatin-gemcitabine was the least costly of the two regimens. Compared with cisplatin-paclitaxel, the gemcitabine-paclitaxel regimen was associated with a significant reduction in mean overall survival time and a 90% probability of higher costs. |
| Relevance to decision-making in England and Wales | The analysis was of limited relevance for the NICE decision problem for this submission. The perspective taken was the Dutch health insurance system rather than the NHS in England and Wales. The outcomes were not reported as incremental cost per quality adjusted life years (QALYs). The resource use and associated costs that were collected in the study may not be generalisable to the UK due to potential variations in patient management patients and patient characteristics as well as differences in relative and absolute prices. |

| **Study** | **Lees (2002) [67]Economic evaluation of gemcitabine alone and in combination with cisplatin in the treatment of non small cell** |
|---|---|

| | |
|---|---|
| | **lung cancer** |
| Aims | To assess the cost-effectiveness of gemcitabine in the treatment of aNSCLC from the perspective of the UK NHS. |
| Methods | Outcomes data (tumour response, PFS and OS) from a trial comparing gemcitabine versus Best Supportive Care (BSC) and gemcitabine plus cisplatin were compared with three "standard" chemotherapies and four "newer " chemotherapies (taxane plus a platinum and vinorelbine plus cisplatin). Drug costs were based on the dosing schedule and the number of treatment cycles given in the trial. Administration costs except for paclitaxel plus cisplatin were assumed to take place in an outpatient setting. Hospital costs associated with febrile neutropenia were included in the cost analysis. Visits to general practitioners were assumed to take place once monthly during treatment and prior to progression and twice monthly after disease progression. |
| Results | In comparison to the "standard" chemotherapies, gemcitabine plus cisplatin was associated with an incremental cost per life year gained of £1,751 versus etoposide plus cisplatin and cost per 1-year survival gain of £5,681 versus mitomycin plus vinblastine plus platinum. The incremental cost per tumour response was £2,032 versus etoposide plus cisplatin, £5,169 versus mitomycin plus ifosfamide plus platinum and £6,240 versus mitomycin plus vinblastine plus platinum. Compared to the newer doublet chemotherapies gemcitabine plus cisplatin was less costly and had the same or better health outcomes. |
| Relevance to decision-making in England and Wales | The cost-effectiveness analysis was conducted in 2000/01 by the manufacturer of gemcitabine as part of their submission to a NICE multiple technology appraisal of the treatment of aNSCLC. The methodology that was adopted is no longer consistent with the NICE reference case. For example, relative treatment benefits between gemcitabine and the "newer" chemotherapies were determined using a naïve indirect comparison. There are no details in the publication that the clinical evidence was systematically reviewed and appraised. Treatment benefits (PFS and OS) were not QALY adjusted. Outcomes were not presented as incremental cost per QALY. Probabilistic sensitivity analysis was not conducted to assess uncertainty in the cost-effectiveness results. |

| **Study** | **Clegg (2002)[68] Clinical and cost effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small cell lung cancer: a systematic review.** |
|---|---|
| Aims | A systematic review and economic evaluation of the clinical and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine regimes for patients with aNSCLC. |
| Methods | Pairwise comparisons between regimens (or BSC) were used to assess the relative treatment efficacies. CMA and CEA versus BSC were conducted to assess whether these treatments offer value for money for the NHS. One-way sensitivity analysis was undertaken to assess the impact on changing the value of key variables on the cost-effectiveness results. |
| Results | Gemcitabine, paclitaxel and vinorelbine regimes were more beneficial as first line treatments for aNSCLC than older regimes or BSC, increasing patient survival by 2 to 4 months against BSC and some comparator regimes. Incremental costs per life year saved (LYS) ranged from £5,206 for vinorelbine plus cisplatin to £14,124 |

| | |
|---|---|
| | for paclitaxel plus cisplatin. |
| Relevance to decision-making in England and Wales | The study was commissioned by NICE in 1999 to help inform their decision on whether paclitaxel, gemcitabine and vinorelbine regimens for the treatment of aNSCLC are a cost-effective use of NHS resources. The methodology adopted is no longer consistent with the current NICE reference case. For example, health outcomes were not QALY adjusted with outcomes being reported as incremental cost per LYS (versus BSC). Probabilistic sensitivity analysis was not conducted to examine uncertainty. The authors also raised methodological concerns over the small size of the trials used in the clinical evidence synthesis and the limited information on patient characteristics that was reported in some of the studies. |

| **Study** | **Dooms (2006)[69] Cost-utility analysis of chemotherapy in symptomatic advanced non-small cell lung cancer** |
|---|---|
| Aims | To evaluate the cost-utility of single agent gemcitabine compared to cisplatin + vindesine as a 1st line treatment for symptomatic aNSCLC. |
| Methods | Clinical outcomes, resource use and health-related quality of life data were prospectively collected in a phase III randomised trial comparing single agent gemcitabine to cisplatin + vindesine. |
| Results | Single agent gemcitabine was €1,522 more costly than cisplatin + vindesine chemotherapy, which was mainly due to the higher drug costs. However, gemcitabine had greater clinical benefit and the resulting ICER for gemcitabine was €13,836/QALY, which the researchers reported is well below internationally accepted benchmarks. |
| Relevance to decision-making in England and Wales | The study was conducted from the perspective of the Swedish health care service and therefore has limited relevance to the NICE decision problem. The methodology used in the study was inconsistent with the NICE reference case (e.g. the method used to elicit utility values were inappropriate, discounting was not applied and the resource use and costs were not generalisable to the UK). |

| **Study** | **Eli Lilly (2009)[70] NICE Single Technology Appraisal for Pemetrexed for the first line treatment of non-small cell lung cancer** |
|---|---|
| Aims | To evaluate the cost-effectiveness of pemetrexed in two subgroups of 1st line patients with aNSCLC (adenocarcinoma and large cell carcinoma) from the perspective of the NHS in England and Wales. |
| Methods | A four health state Markov cost-utility model (response, stable disease, progressive disease and death) was developed to assess the cost-effectiveness of pemetrexed plus cisplatin versus doublet chemotherapy (gemcitabine plus carboplatin, gemcitabine plus cisplatin and docetaxel plus cisplatin). A continuation rule was applied in which patients were separated into those that respond and those that fail to respond to chemotherapy. Patients that responded to treatment were treated for the maximum of 4 cycles whereas those that fail to respond received three cycles. Transition probabilities and treatment tolerability were based on the results of a phase III trial that assessed the efficacy of pemetrexed plus cisplatin versus gemcitabine plus cisplatin. Uncertainty was examined via one-way and probabilistic sensitivity analysis. |
| Results | The base case analysis reported an ICER for pemetrexed plus |

| | |
|---|---|
| | cisplatin versus gemcitabine plus cisplatin of £18,730/QALY in the adenocarcinoma population and £8,035/QALY in the large cell carcinoma population. |
| Relevance to decision-making in England and Wales | The approach adopted by the manufacturer was generally consistent with the NICE reference case. However, the ERG raised some methodological concerns with the submission. For example, the model appeared unable to replicate the results of the trial upon which it was based. It was also noted that vinorelbine plus cisplatin (a less costly doublet chemotherapy regime) had not been included as a relevant comparator. |

## *7.2 De novo economic evaluation(s)*

### 7.2.1 Technology

7.2.1.1 **How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.**

This economic evaluation assesses the use of gefitinib (250mg tablet once daily) as a 1st line treatment for locally advanced or metastatic non-small cell lung cancer (aNSCLC) in patients with positive EGFR-TK mutation status (EGFR M+) who are considered eligible to receive platinum-based doublet chemotherapy.

Treatment with gefitinib will be discontinued when there is evidence of disease progression or the clinician considers the patient is no longer receiving any clinical benefit.

In the IPASS trial, the mean duration of treatment for EGFR M+ patients treated with gefitinib was 8.8 months (median 8.3 months)[71]. No concomitant treatments are required.

7.2.1.2 **Has a treatment continuation rule been assumed?**

A treatment continuation rule has not been assumed.

### 7.2.2 Patients

7.2.2.1 **What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?**

EGFR M+ chemotherapy-naïve patients with aNSCLC who are eligible to receive doublet chemotherapy were included in the economic evaluation.

The licensed indication of gefitinib also covers patients with activating mutations of EGFR-TK who have failed 1st line chemotherapy. However, this population was not included in the NICE decision problem as it was not considered to be of greatest benefit to patients, and ultimately the NHS. AstraZeneca believes the best use of AstraZeneca and NHS resources would be in the development of submission for the 1st line treatment of aNSCLC where there is a higher clinical unmet need.

7.2.2.2 **Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?**

The economic evaluation was carried out in chemotherapy-naïve patients with EGFR-TK mutated aNSCLC. EGFR-TK mutational analysis of tumour tissue is required to identify patients eligible for treatment with gefitinib. The biological plausibility of adopting gefitinib, an oral EGFR-TK inhibitor, for the treatment of this patient subgroup has been discussed in section 4.3.

Sub-group analyses were also conducted based on tumour histology (adenocarcinoma versus non-adenocarcinoma), gender (female versus male) and smoking status (never smoker versus ever smokers). The rationale for these analyses is that EGFR mutations are more frequent in these subgroups (see Appendix 1 for Gefitinib's SmPC). Clinicians may therefore consider using one or more of these patient characteristics to pre-select patients for EGFR testing.

The treatment benefits of using gefitinib to treat these subgroups will be the same as the base case but the cost of EGFR testing will differ due to the differences in mutation frequency.

7.2.2.3 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope**.

All relevant subgroups were considered in the economic evaluation.

7.2.2.4 **At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?**

Chemotherapy-naïve patients with aNSCLC who have tested positive for EGFR TK mutations enter the model with stable disease and are then treated with either gefitinib or doublet chemotherapy. They exit the model when they have died.

The base case analysis includes a comparison in which all chemotherapy naïve patients with aNSCLC are EGFR-TK tested. The analysis assesses the incremental benefit and costs in patients that are confirmed as being EGFR-TK M+.

### 7.2.3 Comparator technology

Gemcitabine, taxanes (paclitaxel or docetaxel) and vinorelbine in combination with either carboplatin or cisplatin are currently recommended by NICE as 1st line treatments for aNSCLC[3].

Given the large number of potential comparators, a pragmatic decision was taken, in collaboration with NICE, to focus the economic evaluation on four doublet chemotherapies that were considered to be of particular relevance to the decision problem.

1. Gemcitabine (1,250mg/$m^2$ on days 1 and 8) plus carboplatin (400mg/$m^2$) (gem/carb) was chosen as the primary comparator for the following reasons:

- Data from the ACTION study and market research data indicate that gemcitabine plus carboplatin is the most frequently used doublet chemotherapy for the 1st line treatment of aNSCLC in the UK, being responsible for an estimated 52%[72] to 67%[10] of patient initiations.

- Carboplatin is often used in preference to cisplatin because it is simpler and less costly to administer (i.e. carboplatin does not require a complex hydration regimen and can be delivered by as a short intravenous infusion over 15min to 60 mins)

2. Gemcitabine (1,250mg/$m^2$ on days 1 and 8) plus cisplatin (75mg/$m^2$ on day 1) (gem/cis). Gem/cis use as a 1st line treatment for aNSCLC is estimated to be between 4% and 14% in the UK[10,72].

3. Paclitaxel (200mg/$m^2$ on day 1) with carboplatin (400mg/$m^2$ on day 1) (pac/carb) was included as a comparator because this regimen was used in IPASS[9] (the phase III trial that demonstrated the clinical benefit of gefitinib in EGFR M+ patients with aNSCLC over double chemotherapy). Outcomes data from this study provided the foundation for the economic model. Data suggests that only around 4% to 5% of chemotherapy naïve patients with aNSCLC are treated with taxane doublet chemotherapy in the UK[10].

4. Vinorelbine (30mg/$m^2$ on day 1 and day 8) plus cisplatin (75mg/$m^2$ on day 1) (vin/cis) was chosen to provide reassurance that low drug cost comparators have not been excluded from the economic analysis. Vin/cis use as a 1st line treatment for aNSCLC in the UK is estimated to be between 3% and 8%[10].

Pemetrexed plus cisplatin was not included as a comparator in the MTC or economic evaluation since at the time the submission was being prepared it was considered unlikely that NICE would recommend this as a 1st line treatment for aNSCLC given the unfavourable NICE ACD assessment[73]. The decision by the Appraisal Committee to recommend Pemetrexed in the first line setting was considered to be too late to be included in any further robust analysis for this submission[74].

### 7.2.4 Study perspective

The perspective of the evaluation was from the NHS and Personal Social Services (PSS). This is consistent with the NICE reference case.

### 7.2.5 Time horizon

A lifetime model with a five-year time horizon was used to estimate the cost-effectiveness of gefitinib in EGFR M+ patients compared to doublet chemotherapy. It has been reported that less than 1% of patients diagnosed with aNSCLC survive beyond 5-years[4].

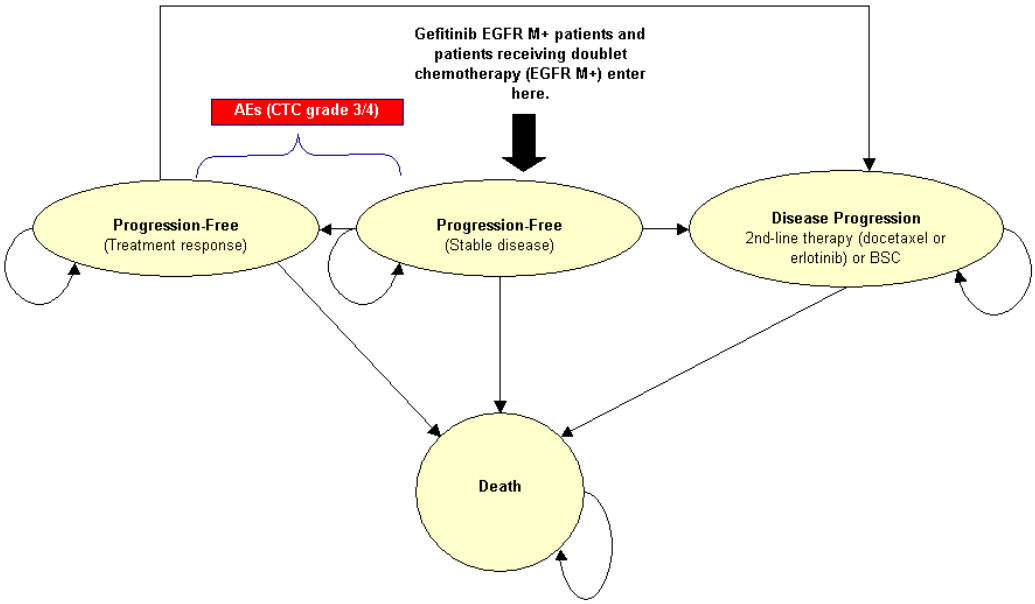
### 7.2.6 Framework

***a) Model-based evaluations***

7.2.6.1 ***Please provide the following.***

An Excel based Markov model (figure 19) was developed to examine the differences in health benefits (QALYs) and overall treatment costs between the competing interventions. Patients entered the model with stable disease and could then transit to one of four different health states: treatment response[2] (TrR), stable disease, disease progression and death.

**Figure 19: Schema for the cost-utility model for the 1st line treatment of aNSCLC**




Moving from stable disease to TrR was associated with a utility gain of 0.0193 (see section 7.2.8.3 for further details of the study used to elicit this value).

It was assumed that TrR did not influence the probability of moving to the disease progression or death health states (i.e. patients that were progression free were assumed to have the same probability of disease progression irrespective of whether they were treatment responders or had stable disease). Although this assumption is weak, a survival analysis of IPASS based on TrR versus stable disease was not available to inform the model.

The odds ratios for treatment response for the indirect comparators: gem/carb EGFR M+, vin/cis EGFR M+ and gem/cis EGFR M+ were sourced from a mixed treatment comparison (MTC) conducted by AstraZeneca (see section 6.6 Indirect/mixed treatment comparisons). These were converted to relative risks (RR) by the method described by Zhang (1998)[75]. The RRs for TrR were applied to the corresponding estimates of treatment response reported for the pac/carb EGFR M+ population in IPASS.

[2] Treatment reponse = complete or partial response

A Weibull (WB) regression model of patient level data from IPASS was used to produce transition probabilities for progression-free (PFS) and overall survival (OS) for pac/carb EGFR M+ (see figures 20 and 21). Covariates included in the WB regression model were: mutation status, gender, performance (O or 1 versus > 1) status and smoking status (never smoker versus ever smoker).

The HR for PFS for gefitinib EGFR M+, determined in the meta-analysis (section 6.5), was applied to the WB PFS regression function for pac/carb EGFR M+ to elicit the PFS transition probabilities for gefitinib (figure 20).

Similarly, the HR for OS for gefitinib EGFR M+ that was reported in IPASS (0.78 95% CI: 0.50 to 1.20) was applied to the WB OS regression function for pac/carb EGFR M+ to determine the OS transition probabilities for gefitinib (figure 21).

**Figure 20: Progression free survival Kaplan Meier (KM) estimates with fitted Weibull survival curves**

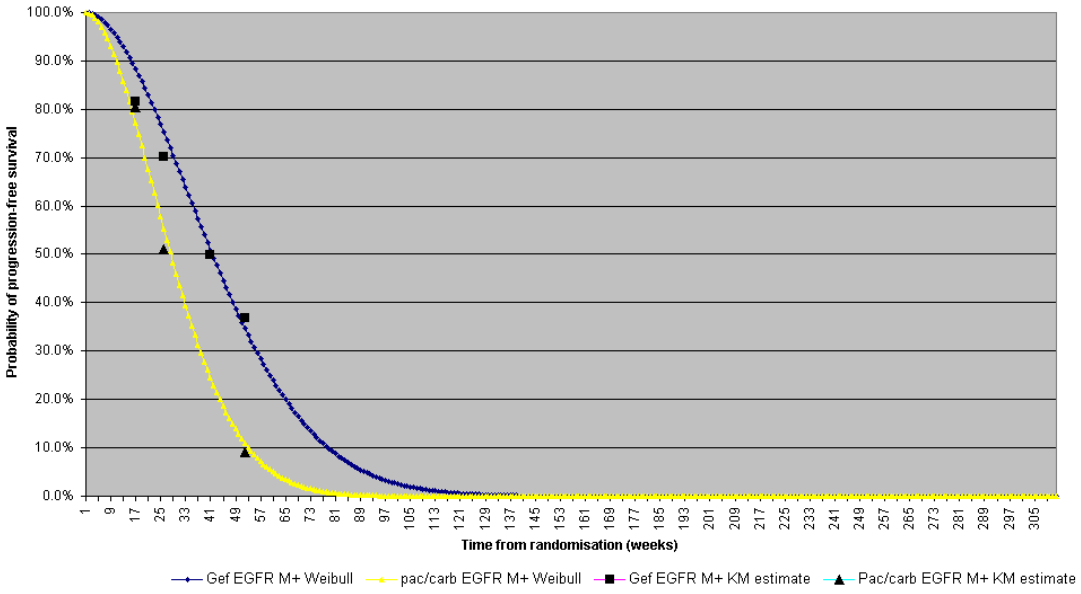
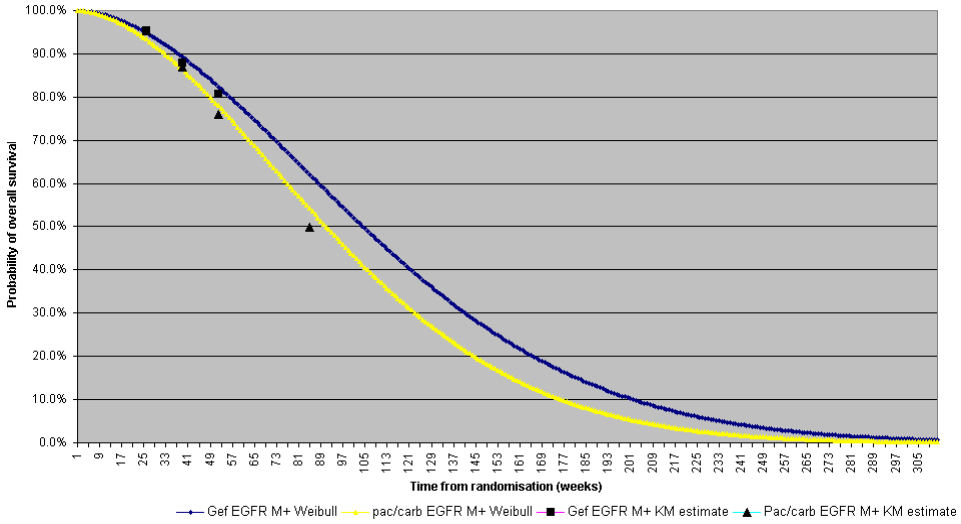


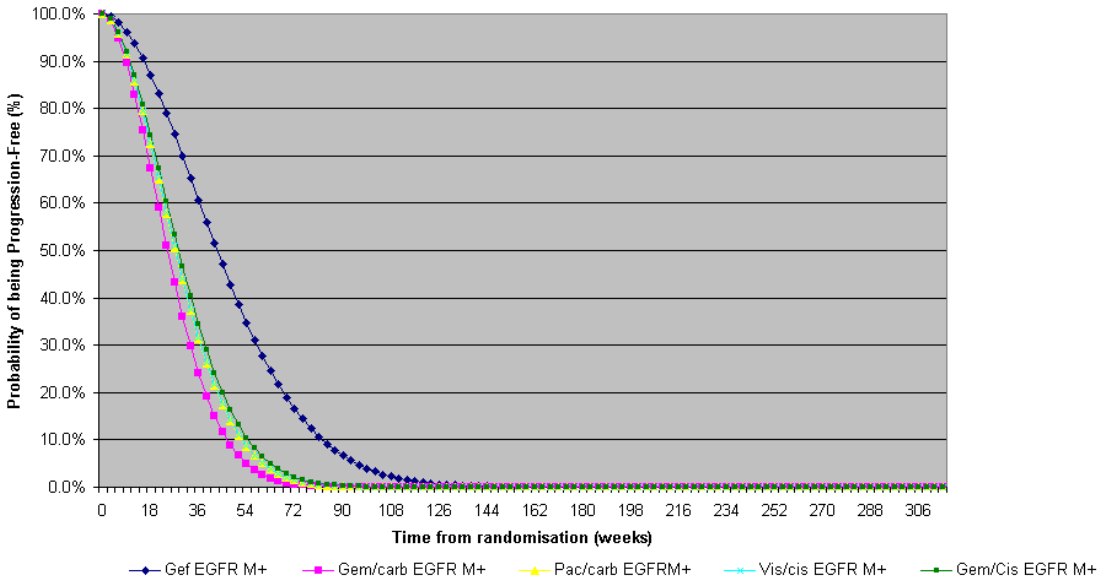
**Figure 21: Overall survival KM estimates with fitted Weibull survival curves[3]**




The proportion of patients transiting to the disease progression health state within a given cycle was estimated as the difference between the proportion of patients being alive at that time point and the proportion of patient being progression-free.

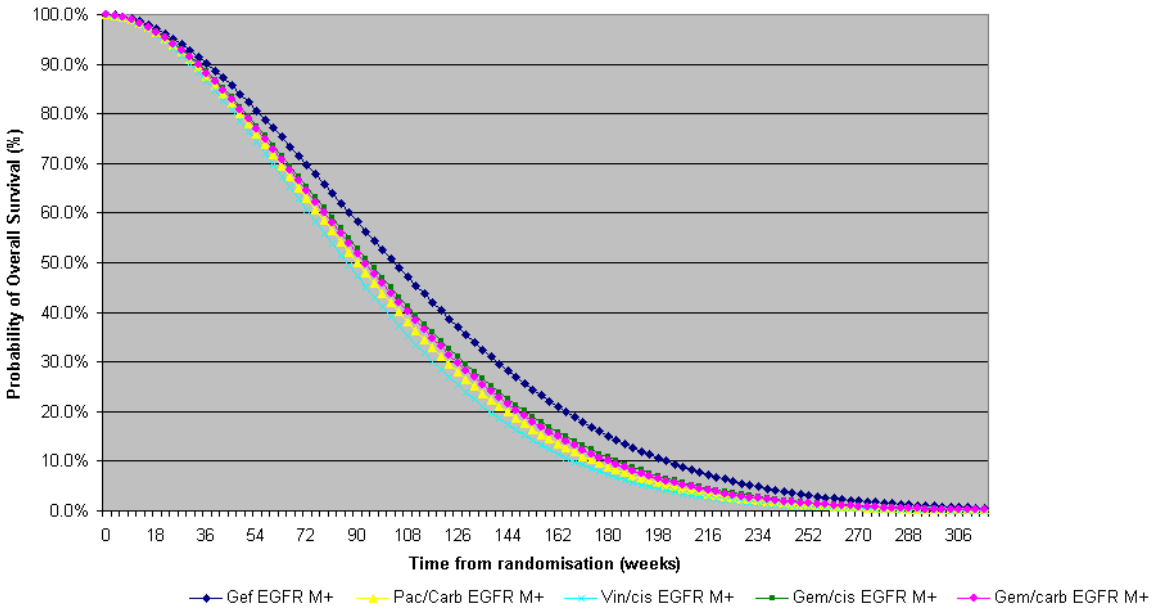
Estimates of the hazard ratios (HR) for PFS and OS for the indirect comparators were sourced from the MTC conducted by AstraZeneca (see table 16). These hazard ratios were applied to the corresponding Weibull functions for pac/carb EGFR M+ to generate the probabilities for transiting between the health states at each cycle of the model (figures 22 and 23).

**Figure 22: PFS plots using fitted Weibull survival function estimates**




[3] Overall survival data is based on a small number of events. A post hoc analysis was conducted on OS after observing the PFS results (see section 6.4) The HR for OS was numerically in favour of gefitinib in M+ patients but not statistically significant between the treatment arms (HR 0.776, 95% CI: 0.5 to 1.202). A final analysis of the survival data is anticipated in Q2 2010.

**Figure 23: OS plots using fitted Weibull survival function estimates**




CTC grade 3/4 adverse events (AE) for gefitinib EGFR M+ and pac/carb EGFR M+ that occurred in 3% or more of patients were obtained from IPASS[27] (table 20). The RRs of an AE occurring for the indirect comparators were sourced from the MTC (see section 6.6) and applied to the pac/carb EGFR M+ AE incidence data from IPASS.

**Table 20: CTC grade 3/4 AE included in cost-effectiveness analysis (IPASS pac/carb M+ as baseline for the indirect comparators when ever possible)**

| Adverse Event | Gefitinib EGFR M+ | Gem/carb EGFR M+ | Pac/carb EGFR M+ | Vin/cis EGFR M+ | Gem/cis EGFR M+ |
|---|---|---|---|---|---|
| Neutropenia | 0.0% | 29.8% | 33.3% | 52.8% | 25.9% |
| Febrile Neutropenia | 0.0% | 1.0% | 3.9% | 7.4% | 1.6% |
| Fatigue* | 0.0% | 2.3% | 2.3% | 3.6% | 3.3% |
| Nausea & Vomiting | 0.0% | 7.3% | 4.7% | 17.0% | 21.2% |
| Diarrhoea | 5.3% | 0.8% | 0.8% | 1.1% | 0.9% |
| Hair Loss* | 1.2% | 31.6% | 31.6% | 31.6% | 31.6% |
| Rash | 2.3% | 0% | 0% | 0% | 0% |
| Anaemia | 1.5% | 56.7% | 9.3% | 22.1% | 21.7% |

* The MTC was unable to provide odds ratios for chemotherapy induced hair loss for the indirect comparators and a meaningful odds ratio for gem/carb induced fatigue and diarrhoea. The same incidence as pac/carb has therefore been assumed for these AEs.

A 21-day Markov cycle length was adopted as this reflects the length of time between cycles of doublet chemotherapy and was also considered the shortest interval over which clinicians would observe a change in the course of the disease or symptoms in clinical practice.

Patients with progressive disease received either BSC or 2nd line treatment followed by BSC.

The key variables and model assumptions that were used in the cost-effectiveness analysis are presented in tables 21 and 22. The ranges (distributions) are provided in section 7.2.11.3.

**Table 21: Model Variables and their Source**

| Model Variable | Value | Source |
|---|---|---|
| **Discount rates** | | |
| Costs | 3.5% | NICE reference case |
| Benefits | 3.5% | NICE reference case |
| **Patient characteristics** | | |
| EGFR M+ (overall population) | 16.6% | Rosell (2009)[76] |
| EGFR M+ (adenocarcinoma) | 16% | Gefitinib SPC (See Appendix 1) |
| EGFR M+ (non-adenocarcinoma) | 3% | Gefitinib SPC (See Appendix 1) |
| EGFR M+ (female) | 17% | Gefitinib SPC (See Appendix 1) |
| EGFR M+ (male) | 6% | Gefitinib SPC (See Appendix 1) |
| EGFR M+ (never smoker) | 40% | Gefitinib SPC (See Appendix 1) |
| EGFR M+ (ever smokers) | 7% | Gefitinib SPC (See Appendix 1) |
| Post-progression active treatment | 61% | IPASS |
| Mean Body Surface Area ($m^2$) | 1.82 | ERG report (2009)[77] |
| G-CSF use of prophylaxis of neutropenia | 21.7% | IPASS (2009) |
| **Treatment Response:** | | |
| Gefitinib EGFR M+ | 71.2% | IPASS[9] |
| Pac/carb EGFR M+ | 47.3% | IPASS[9] |
| Gem/carb EGFR M+ | 43.3% | MTC (section 6.6) |
| Vin/cis EGFR M+ | 49.5% | MTC (section 6.6) |
| Gem/cis EGFR M+ | 50.8% | MTC (section 6.6) |
| **Hazard Ratio PFS:** | | |
| Gefitinib EGFR M+ | 0.43 | Meta-analysis (section 6.5) |
| Gem/carbo EGFR M+ | 1.23 | MTC (section 6.6) |
| Vin/cis EGFR M+ | 0.99 | MTC (section 6.6) |
| Gem/cis EGFR M+ | 0.92 | MTC (section 6.6) |
| **Hazard Ratio OS:** | | |
| Gefitinib EGFR M+ | 0.78 | IPASS[9] |
| Gem/carbo EGFR M+ | 0.95 | MTC (section 6.6) |
| Vin/cis EGFR M+ | 1.08 | MTC (section 6.6) |
| Gem/cis EGFR M+ | 0.92 | MTC (section 6.6) |
| **Mean Utility Values** | | |
| Baseline utility (stable disease no AEs) | 0.6532 | Nafees (2008)[78] |
| Treatment response (increment) | 0.0193 | Nafees (2008)[78] |
| **Utility Decrements** | | |
| - Disease progression | -0.1798 | Nafees (2008)[78] |
| - Progression-free iv therapy | -0.0425 | ERG report (2006)[79] |

| | | |
|---|---|---|
| - Progression-free oral therapy | -0.0139 | ERG report (2006)[79] |
| CTC grade 3/4 AE | | |
| - Febrile neutropenia | -0.0900 | Nafees (2008)[78] |
| - Neutropenia | -0.0897 | Nafees (2008)[78] |
| - Fatigue | -0.0735 | Nafees (2008)[78] |
| - Nausea & vomiting | -0.0480 | Nafees (2008)[78] |
| - Diarrhoea | -0.0468 | Nafees (2008)[78] |
| - Hair loss (grade 2) † | -0.0450 | Nafees (2008)[78] |
| - Rash | -0.0325 | Nafees (2008)[78] |
| - Anaemia | -0.0735 | Eli Lilly (2009)[78] |
| **Costs** | | |
| Gefitinib (single fixed payment per patient) | [redacted] | AstraZeneca Commercial in Confidence |
| EGFR mutation test (per test) | [redacted] | Lab 21 Commercial Contract |
| Gefitinib patient monitoring (per month) | £86 | Reference costs (2007/08)[80] |
| Drug acquisition gem/carb (per cycle) | £999 | BNF (2009)[81], Dictionary of Medicines and Devices[82] |
| Drug acquisition pac/carb (per cycle) | £1,489 | BNF (2009)[81] |
| Drug acquisition vin/cis (per cycle) | £403 | BNF (2009)[81] |
| Drug acquisition gem/cis (per cycle) | £795 | BNF (2009)[81], Dictionary of Medicines and Devices[82] |
| Administration gem/carb (per cycle) | £307 | Reference costs (2007/08)[80] |
| Administration pac/carb (per cycle) | £153 | Reference costs (2007/08)[80] |
| Administration vin/cis (per cycle) | £527 | Reference costs (2007/08)[80] |
| Administration gem/cis (per cycle) | £527 | Reference costs (2007/08)[80] |
| Drug acquisition g-CSF (per patient treated)‡ | £1,284 | BNF (2009)[81] |
| Grade 3/4 neutropenia | £92.80 | ERG Addendum (2007)[83] |
| Grade 3/4 febrile neutropenia | £2,286 | ERG Addendum (2007)[83] |
| Grade 3/4 fatigue | £39 | Eli Lilly (2009)[70] |
| Grade 3/4 nausea and vomiting | £701 | Eli Lilly (2009)[70] |
| Grade 3/4 diarrhoea | £867 | Eli Lilly (2009)[70] |
| Grade 3/4 rash | £117 | Roche (2006)[84] |
| Grade 3/4 anaemia | £615 | Eli Lilly (2009)[70] |
| NHS patient transport service (per journey) | £28 | Reference costs (2007/08)[80] |
| Best support care (BSC) (per cycle) | £600 | Clegg (2002)[68] |
| 2nd line therapy followed by BSC (per cycle) | £1,022 | ERG report (2006)[79] |

†CTC grade 2 hair loss = pronounced hair loss. * PS = performance status ‡ granulocyte-macrophage colony stimulating factor (filgrastim).

## Table 22: Modeling assumptions and justification

| Assumption | Description | Justification |
|---|---|---|
| Incidence of EGFR M+ in aNSCLC patients in UK | EGFR testing is not routinely conducted in patients with aNSCLC in the UK. The incidence of EGFR mutations in the UK is therefore unknown.<br><br>An EGFR M+ incidence of 16.6% has been assumed for the UK population. | The figure of 16.6% was sourced from a large (n=2,105) EGFR mutation screening study conducted by the Spanish Lung Cancer Group [76].<br><br>While it is accepted that there may be differences between the Spanish and UK patient populations this figure is considered the best available estimate for a Western European population. |
| Pre-selection of patients for EGFR testing based on clinical characteristics | In the base case analysis it has been assumed that every chemotherapy naïve patient diagnosed with aNSCLC will be eligible for EGFR testing.<br><br>However, clinical characteristics of adenocarcinoma, female gender and never smoker have all been found to be independent predictors of EGFR M+ (see Appendix 1).<br><br>In a multivariate analysis of 786 Caucasian patients from gefitinib studies reported that: 16% (63/396) of patients with adenocarcinoma were EGFR M+ versus 3% (12/390) of patients with non-adenocarcinoma histology, 17% of females (40/235) were EGFR M+ versus 6% (35/551) of males and 40% (28/70) of never smokers were EGFR M+ versus 7% (47/716) of ever smokers.<br><br>The Spanish Lung Cancer Group[76] screening study reported an EGFR M+ frequency of: 17.3% (95% CI 15.5% to 19.2%) in patients with adenocarcinoma, 30% (95% CI 26.9% to 33.2%) in females versus 8.2% (95% CI 6.8% - 9.9%) in men and 37.7% (95% CI 34% to 41.7%) in never smokers versus 5.8% (4.0 to 8.6%) in current smokers. | Although selecting patients for EGFR testing based on one or more of the predictive clinical characteristics of EGFR M+ would significantly reduce the costs of identifying patients eligible for gefitinib this practice is likely to raise equity concerns among health care professionals in NHS in England & Wales and was not considered in the base case analysis. |
| Best supportive care (BSC) | It is assumed that 39% of patients with disease progression after 1st line therapy will receive BSC only. | In IPASS, 39% of EGFR M+ patients treated with pac/carb received no further active treatment following disease progression.<br><br>Data for the proportion of EGFR M+ patients randomised to gefitinib that received BSC post-progression are currently unavailable. A figure of 39% |

| Assumption | Description | Justification |
|---|---|---|
| | | has been assumed. |
| Post-progression active treatments | It is assumed that 61% of patients would receive an active treatment post-progression.<br><br>It is assumed that EGFR M+ patients progressing after 1st line doublet chemotherapy would be treated with either erlotinib or docetaxel.<br><br>EGFR M+ patients treated with 1st line gefitinib would most likely receive docetaxel on progression if considered suitable. | Data from IPASS indicated that 61% of EGFR M+ patients with disease progression in the pac/carb treatment arm received either another chemotherapy or an EGFR-TKI. Post-progression treatment data for gefitinib is currently unavailable, a figure of 61% has been assumed.<br><br>Docetaxel and erlotinib are currently the only 2nd line treatments for aNSCLC that are recommended by NICE. The two treatments have been assumed to be equally effective and provided to the NHS at the same overall cost. |
| NHS funded transportation to and from the chemotherapy sessions. | 50% of patients receiving doublet chemotherapy will require NHS funded transport. | The ERG for the erlotinib STA submission considered that 50% of patients with aNSCLC receiving docetaxel would require NHS funded transport to hospital for their chemotherapy[79]. It is not implausible to assume a similar proportion of patients receiving doublet chemotherapy would require help with transport to and from the hospital. |
| Relative treatment effects (ORR, PFS and OS) for the indirect comparators in an EGFR M+ population | No direct RCT data was available at the time the submission was prepared to estimate the treatment benefit of gefitinib versus gemcitabine or vinorelbine doublet chemotherapy in an EGFR M+ population. It has been assumed that the relative treatment effects derived from the MTC (see section 6.6) in an untested population could be applied to the pac/carb EGFR M+ PFS and OS data. | The approach that has been adopted is consistent with the NICE guidance for evidence synthesis in the absence of head to head RCT data. |
| Maximum number of doublet chemotherapy cycles | Doublet chemotherapy was restricted to a maximum of 6 cycles. | The IPASS clinical trial protocol restricted the number of doublet chemotherapy cycles to a maximum of 6. |

| Assumption | Description | Justification |
|---|---|---|
| Inclusion of adverse events | With the exception of hair loss and neurotoxicity, only grade 3/4 AEs that occurred in > 3% of patients were included in the economic evaluation. | The assumption was considered to capture all the main drivers of cost and HRQoL. It is also consistent with the assumptions used in previous NICE STA submissions for aNSCLC[70,84].<br><br>Chemotherapy induced hair loss was included in the economic evaluation since it has been reported to have a detrimental impact on HRQoL[78,85]. This AE can be particularly distressing for female patients with aNSCLC[86] who may to consider refusing therapy. |
| Utility estimates for 1st line treatment of aNSCLC | No studies were found in the literature that provided utility values for the 1st line treatment of aNSCLC that would meet the NICE reference case.<br><br>Utility estimates for the 1st line treatment of aNSCLC were sourced from a UK study that used standard gamble (SG) to elicit health state preferences for the 2nd line treatment of aNSCLC for members of the public[78]. | The decision to use the utility estimates from the Nafees study was made after a systematic search of the published literature (see section 7.2.8.3) |
| Utility decrement for grade 3/4 AEs | The disutility associated with grade 3/4 AEs was applied for a single cycle in the model (i.e. 21 days).<br><br>Grade 3/4 anaemia was assumed to have the same disutility as grade 3/4 fatigue. | The health states developed to derive utilities for the 2nd line treatment of aNSCLC were designed to describe a 3-week period. However, it is acknowledged that certain AEs (e.g. hair loss, fatigue, anaemia, rash) may have a deleterious effect on HRQoL throughout the course of treatment. The model may therefore underestimate the impact of these AEs on HRQoL. |
| Cost of EGFR test | A unit cost of [redacted] per EGFR test has been assumed in the base case analysis. | [redacted]<br>Greater competition among commercial and NHS laboratories and economies of scale are likely to see the cost of the test fall when it becomes accepted practice in the treatment of aNSCLC. |
| Average body surface (BSA) area used to estimate the cost of chemotherapy drugs. | A mean BSA of 1.82/$m^2$ has been assumed in the base case analysis. | The ERG that appraised pemetrexed as a 1st line treatment for aNSCLC used this value to estimate the cost of doublet chemotherapy [70]. |

| Assumption | Description | Justification |
|---|---|---|
| Gefitinib patient monitoring | It is assumed that gefitinib treated patients would be reviewed by a clinician on a monthly basis to evaluate treatment response. Patients with signs of disease progression would discontinue the drug. The tariff (£86) for a consultant led follow-up face to face attendance was used in the base case analysis (HRG 800). | This assumption was considered plausible and consistent with medical opinion. |
| Doublet chemotherapy patient monitoring | It was assumed that patients undergoing chemotherapy would not require additional monitoring during their course of therapy.<br><br>Patients that remain progression-free after they had received the maximum cycles of chemotherapy were assumed to receive the same frequency of monitoring as the gefitinib treated patients. | Medical opinion considered this a reasonable assumption to make. |
| Concomitant medications and pre-chemotherapy blood tests | The costs of concomitant medications given to patients receiving doublet chemotherapy (e.g. steroids, antihistamines, paracetamol etc) and blood tests are assumed to be captured in the HRGs for the delivery of chemotherapy. | Concomitant medications and blood tests are relatively inexpensive and would have little impact on the cost-effectiveness results. |
| Dose of carboplatin administered with gemcitabine or paclitaxel | Carboplatin is administered on an individual patient basis to achieve a target plasma concentration (typically AUC 5.0 to 6.0). In this economic evaluation it has been assumed that patients receive an average dose of carboplatin of 400mg/$m^2$. | This assumption is consistent with the carboplatin product licence that recommends a dose of 400mg/$m^2$ in previously untreated patients with normal renal function[87] |
| Adverse event related treatment discontinuations | AE related treatment discontinuations are not included in the economic model. | PFS and OS for gefitinib in EGFR M+ patients and pac/carb EGFR M+ were analysed on an Intention To Treat (ITT) basis. Patients discontinuing treatment due to AEs are included within the ITT population. It would be inappropriate to consider patients discontinuing treatment a separate group in the model, as they have been included within the survival analyses and impact on the respective outcomes. |

### 7.2.6.2 **Why was this particular type of model used?**

The Markov model developed for the submission allowed all the important clinical and cost related events to be captured between the competing interventions over a lifetime horizon. In particular, the model enables:

- An extrapolation of overall survival beyond the IPASS interim analysis
- Comparisons of the relative treatment effects and costs of gefitinib EGFR M+ *versus* the indirect comparators gem/carb EGFR M+, vin/cis EGFR M+ and gem/cis EGFR M+ to be made

#### 7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure of the gefitinib Markov model is similar to those previously used to inform decision problems related to the treatment of lung cancer[70,84,88,89]. In the model, patients making one-way transitions from the progression free health states to disease progression and ultimately death, which reflects the natural progression of aNSCLC.

#### 7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The main sources of information used to develop and inform the structure of the gefitinib Markov model were IPASS[9], the systematic review and mixed treatment comparison (MTC) reported in section 6.6 , the systematic review of the health economic literature (see 7.1.1) and the recent NICE STA submissions for pemetrexed[70] and erlotinib[84] for the treatment of aNSCLC

#### 7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The gefitinib Markov model reflects all the essential features of the 1st line treatment of aNSCLC, with the exception that grade 3/4 AEs are assumed to occur in the first cycle only. The variable risks of the AEs occurring according to the number of previous chemotherapy cycles were not captured in the model. This was due to limitations in the AE reporting for the indirect comparators. The incidence of grade 3/4 AEs was sporadically reported (i.e. % of patients that experienced a given AE) and no data on event rates were provided (i.e. number of AEs experienced per patient).

In addition there was insufficient data to model the probability of patients experiencing multiple AEs (e.g. fatigue, hair loss and nausea & vomiting) and estimate the subsequent decrement in their health-related quality of life.

#### 7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

Not applicable.

#### 7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction was incorporated in the model.

7.2.6.8 **Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?**

Overall survival was extrapolated beyond the IPASS data cut off (DCO) for the primary analysis since at the time of submission only 450 deaths has occurred (450/1217, 37% maturity. Follow up of patients will continue and the final analysis conducted when 944 deaths have occurred[9]. The interim OS survival analysis for gefitinib EGFR M+ versus pac/carb EGFR M+ in IPASS provides a hazard ratio in favour of gefitinib of 0.78, 95% CI: 0.50 to 1.20. It is anticipated that the final overall analysis will be available in Q2 2010.

A Weibull regression analysis of IPASS was therefore conducted to model the costs and outcomes beyond the IPASS trial follow-up period.

### 7.2.7 Clinical evidence

7.2.7.1 **How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline**.

The baseline risks of disease progression and overall survival for gefitinib EGFR M+ and pac/carb EGFR M+ were estimated using a Weibull regression model of IPASS (see section 7.2.6.1). The Weibell regression model for pac/carb EGFR M+ was used as a baseline to generate transition probabilities for the indirect comparators gem/carb EGFR M+, vin/cis EGFR M+ and gem/cis EGFR M+.

7.2.7.2 **How were the relative risks of disease progression estimated?**

The hazard ratios for disease progression for the indirect comparators were estimated using data from the MTC reported in section 6.6 table 9.

7.2.7.3 **Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?**

Not applicable.

7.2.7.4 **Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?**

The HRQoL and cost impact of CTC grade 3/4 febrile neutropenia, neutropenia, fatigue, nausea and vomiting, diarrhoea, hair loss, rash and anaemia were included in the economic evaluation. In addition, patient preference (utility) for oral as opposed to intravenous treatments for end-stage cancer was also captured

7.2.7.5 **Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?**

No

7.2.7.6 **What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?**

There are no outstanding assumptions regarding the clinical evidence provided in this submission.

### 7.2.8 Measurement and valuation of health effects

7.2.8.1 **If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?**

Health effects were expressed as QALYs in the economic evaluation.

7.2.8.2 **Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.**

The following health effects were measured and valued in the economic evaluation: progression-free survival, treatment response, post-progression survival, CTC grade 3/4 AEs (neutropenia, febrile neutropenia, fatigue, nausea & vomiting, diarrhoea, rash, anaemia) and partial or complete hair loss, route of administration (intravenous *versus* oral).

7.2.8.3 **How were health effects measured and valued?**

EQ-5D was not used to measure HRQoL in the IPASS trial. Utility values for the health states described in the model were therefore sourced from the published literature using search filters provided on the York University online resource (see Appendix 10.3).

Thirty abstracts were identified as being potentially relevant. Following further review, the abstracts that had the highest potential for providing utility estimates for the 1st line treatment of aNSCLC and would fulfill the NICE reference case were ordered as full text (n=3)[33,69,90]

All three papers were rejected for the following reasons:

- Belani (2006)[90] – EQ-5D Visual Analogue Scale (VAS) was used to assess HRQoL in chemotherapy naïve patients with aNSCLC. Insufficient details were provided in the paper to derive robust utility estimates that could be used to inform the economic model[4].

- Dooms (2006)[69] – HRQoL of patient with aNSCLC treated with gemcitabine versus vindesine + cisplatin was measured using a

[4] It was interesting to note that this study found that patients treated with a taxane regimen had better HRQoL than vinorelbine + cisplatin, as assessed by the EQ-5D and the LCSS (a disease specific instrument).

disease specific instrument (Lung Cancer Symptom Score (LCSS)) rather than the EQ-5D. It was not possible to derive utility estimates for the model from the limited details given in the paper.

- Helbekkmo (2007) [33] – a disease specific instrument was used to measure HRQoL (QLQ-C30) in this study of vinorelbine/carboplatin vs gemcitabine/carboplatin in aNSCLC. Limited details were provided on the impact of doublet chemotherapy on HRQoL. It was not possible to derive utility estimates for the model from this paper.

An ASCO conference abstract of the ACTION study[91] was referenced in an ERG addendum [83]that had the potential to provide utility estimates for the model. This was a European observational study that elicited HRQoL values using EQ-5D for 1st line patients with aNSCLC. 193 patients from the UK participated in the study. Unfortunately, insufficient data were provided in the abstract to inform the model and a full publication of the study has yet to be produced.

In the absence of other relevant utility estimates, a pragmatic approach was taken to adopt utility estimates from a UK study by Nafees (2008)[78] that elicited societal preferences for the 2nd line treatment of aNSCLC.

In the Nafees study, telephone interviews with a group of oncologists (n=4) and oncology specialist nurses (n=4) were used to derive health state descriptions of the symptom burden and six grade 3/4 drug related toxicities and hair loss associated with the treatment of aNSCLC.

Members of the general public (n=105) were then interviewed and asked to value the health state descriptions using the VAS and Standard Gamble (SG) utility methods.

The utility values obtained from this study are provided in table 21.

It was interesting to note that the 2nd line aNSCLC utility estimate for the base state (stable disease no toxicity) of 0.654 reported by Nafees was no dissimilar to the EQ-ED derived value of 0.64 that was obtained from 1st line patients with aNSCLC in the UK that participated in the ACTION study. This finding gives the approach that has been adopted some degree of validity.

Utility estimates associated with the delivery of treatment (oral vs intravenous) were not reported by Nafees (2008)[78]. The utility values were therefore sourced from the ERG report of erlotinib for the 2nd line treatment of aNSCLC[70]. In this report, the ERG used a linear transformation to rescale EQ-5D VAS scores elicited from a UK study (n=154)[84] so that death was mapped onto a value of zero.

7.2.8.4 **Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11)**.

In IPASS, health-related quality of life was measured using the total score and Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire[9].

Significantly more gefitinib EGFR M+ patients experienced clinically important improvements in HRQoL as measured by the FACT-L total score compared with paclitaxel/carboplatin EGFR M+, 70.2% versus 44.5%, p<0.0001 (table 23). This was finding was also observed when HRQoL was assessed using the TOI.

In EGFR M+ patients treated with gefitinib, the mean changes in HRQoL from baseline showed meaningful improvement by week 1 for FACT-L (+6) and by week 3 for TOI (+6) suggesting a relatively rapid response.

By way of contrast, in the pac/carb EGFR M+ group there was a meaningful drop in HRQoL at week 1 (–6 in FACT-L and TOI). This effect was not apparent at week 3, but, after week 3, there was no further improvement in HRQoL as measured by either the FACT-L or TOI.

**Table 23: Improvement[a] rates for HRQoL in the EGFR M+ population**

| HRQoL measure | Gefitinib | | Paclitaxel/carboplatin | | Odds ratio | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| | N | n (%) Improved | N | n (%) Improved | | | |
| FACT-L | 131 | 92 (70.2%) | 128 | 57 (44.5%) | 3.010 | 1.786 to 5.073 | <0.0001 |
| TOI | 131 | 92 (70.2%) | 128 | 49 (38.3%) | 3.955 | 2.329 to 6.714 | <0.0001 |

[a]A clinically relevant improvement was pre-defined as a 6-point improvement for FACT-L and TOI

Time to worsening in HRQoL (as measured by FACT-L and TOI) in the EGFR M+ population in IPASS were substantially longer in the gefitinib arm compared with the pac/carb arm (table 24).

**Table 24: Summary of time to worsening in HRQoL in the EGFR M+ population**

| HRQoL measure | Treatment | N | Percentage worsened | Median (months) | 95% CI |
|---|---|---|---|---|---|
| FACT-L | Gefitinib | 131 | 33.6% | 15.6 | 11.0 to NC* |
| | Paclitaxel/carboplatin | 128 | 57.8% | 3.0 | 1.5 to 5.3 |
| TOI | Gefitinib | 131 | 31.3% | 16.6 | 11.1 to NC* |
| | Paclitaxel/carboplatin | 128 | 56.3% | 2.9 | 1.5 to 7.0 |

* NC = not calculated

The Kaplan-Meier curve for time to worsening in FACT-L total score and TOI score in the M+ population from IPASS are shown in figures 24 and 25

**Figure 24: Kaplan-Meier curves for time to worsening of FACT-L total score EGFR M+ population**

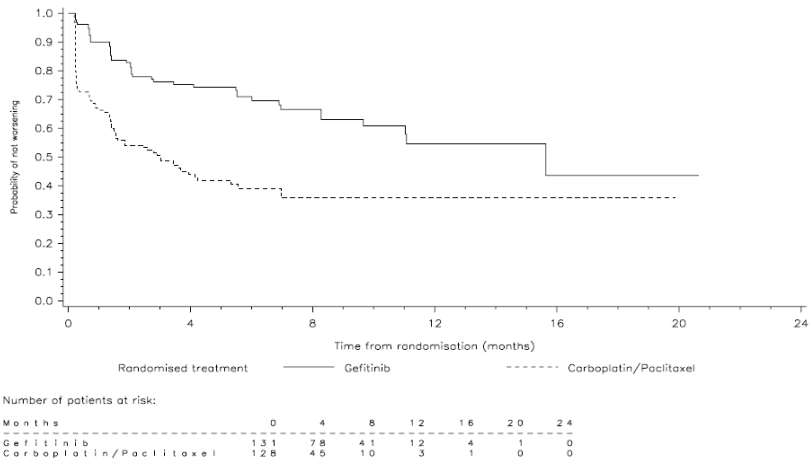
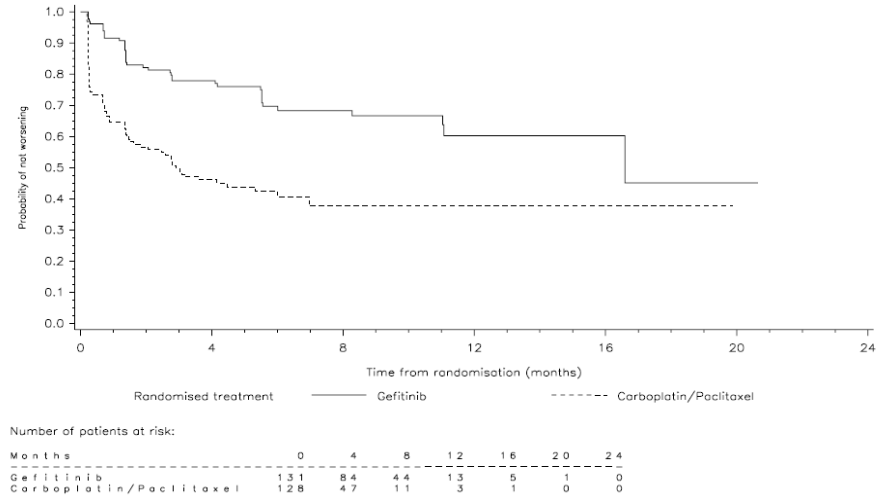



**Figure 25: Kaplan-Meier curves for time to worsening of TOI score EGFR M+ population**




#### 7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

The disutility associated with grade 3/4 AEs that occurred at a frequency < 3% and grade I/2 AEs were excluded from the analysis.

The HRQoL of the patient's carer(s) and/or family has also not been factored into the analysis, as this is not included within the NICE reference case.

### 7.2.9 Resource identification, measurement and valuation

#### 7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

NHS resources included in the evaluation are as follows (see Table 21 for the values, and sources):

- Medication (see 7.2.9.2 for details of the cost calculations for chemotherapy and 7.2.9.6 for details of the gefitinib single payment access (SPA) scheme)
- Delivery of chemotherapy

- EGFR testing
- Patient monitoring
- NHS transport service
- Grade 3/4 AE management
- Best supportive care (BSC)
- Post-progression active treatment

7.2.9.2 ***How were the resources measured?***

- Medication (table 24 and 25):

The resource use and drug costs for doublet chemotherapy were based on an average body surface area of 1.82$m^2$ and a maximum number of treatment cycles of 6.

Chemotherapy costs are based on NHS list prices given in the BNF 57 March 2009 with the exception of gemcitabine which lost its patent exclusivity in March 2009. The NHS Dictionary of Medicines and Devices was accessed in August 2009 to obtain the current cost of generic gemcitabine. No wastage is assumed in the cost calculations. It was assumed that the average dose of carboplatin used to treat patients with aNSCLC was 400mg/$m^2$. The least expensive vial size and/or manufacturer were used to determine the cost of chemotherapy.

**Table 24: Chemotherapy unit costs**

| | Unit cost per vial | Cost per mg | Dose | Cost per dose |
|---|---|---|---|---|
| Gemcitabine (1,000mg vial) | £159.49 | £0.16 | 1,250mg/$m^2$ (Day 1 & 8) | **£363** |
| Paclitaxel (300mg vial) | £1,001.72 | £3.34 | 200mg/$m^2$ (Day 1) | **£1,215** |
| Vinorelbine (50mg vial) | £153.98 | £3.08 | 30mg/$m^2$ (Day 1 & 8) | **£168** |
| Carboplatin (450mg vial) | £168.85 | £0.38 | 400mg/$m^2$ (Day 1) | **£273** |
| Cisplatin (50mg) | £24.50 | £0.49 | 75mg/$m^2$ (Day 1) | **£67** |

**Table 25: Doublet chemotherapy costs per 21-day cycle**

| | Cost per cycle | Total cost per cycle |
|---|---|---|
| Gemcitabine + carboplatin | (£363 *2) + £273 | **£999** |
| Paclitaxel + carboplatin | £1,215 + £273 | **£1,489** |
| Vinorelbine + cisplatin | (£168 * 2) + £67 | **£403** |
| Gemcitabine + cisplatin | (£363 *2) + £67 | **£795** |

- Delivery of chemotherapy

It is assumed that all relevant resource use associated with the delivery of chemotherapy in England & Wales is captured in the HRG codes SB12Z,

SB14Z and SB15Z and reflected in the National Schedule for Reference Costs for 2007/08 (see tables 26 and 27)[80].

**Table 26: National schedule for reference costs (2007/08)[80]**

| HRG code | Description | Unit Cost |
|---|---|---|
| SB12Z | Deliver simple parenteral chemotherapy at first attendance. Outpatient chemotherapy delivery. | £153 |
| SB14Z | Deliver complex chemotherapy including prolonged infusional treatment at first attendance. Chemotherapy delivery day case and regular day/night. | £307 |
| SB15Z | Deliver subsequent elements of chemotherapy cycle. Outpatient chemotherapy delivery. | £154 |
| SB15Z | Deliver subsequent elements of chemotherapy cycle. Chemotherapy delivery day case and regular day/night. | £220 |

**Table 27: Unit costs for the delivery of doublet chemotherapy for aNSCLC (per cycle)**

| Comparator | Resource | Cost per cycle |
|---|---|---|
| Gem/carb | 1 x SB12Z (outpatient) + 1 x SB15Z (outpatient) | £307 |
| Pac/carb | 1 x SB12Z (outpatient) | £153 |
| Vin/cis | 1 x SB14Z (Day case and regular day/night) + SB15Z (Day case and regular day/night) | £527 |
| Gem/cis | 1 x SB14Z (Day case and regular day/night) + SB15Z (Day case and regular day/night) | £527 |

- EGFR testing

Although EGFR testing is not currently routinely conducted on tissue biopsies for patients with aNSCLC in the UK, a number of NHS and commercial diagnostic laboratories have been identified that have the capacity to provide this service.

[redacted]

[redacted]

It is likely the cost of the EGFR testing will be reduced as more suppliers enter the market, biopsy techniques improve, new testing techniques become available (including the detection of EGFR mutation from patient blood samples[92]) and economies of scale are achieved.

**Table 28: [redacted]**

| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
|---|---|---|---|---|---|

- Patient monitoring

It has been assumed that gefitinib treated patients will be reviewed by an oncologist on a monthly basis. The reference cost for HRG800 (consultant led follow-up attendance, non-admitted face-to-face) of £86 was used as a cost estimate for this resource[80].

For the comparator treatments, it has been assumed that patients that are progression-free after receiving the maximum number of chemotherapy cycles would incur the same monitoring costs as gefitinib treated patients.

- NHS Transport Service

The ERG appraisal team for erlotinib in the 2nd line treatment for aNSCLC considered it reasonable to assume that 50% of patients receiving docetaxel would require NHS transport to and from the hospital[83].

This assumption was also considered applicable to patients receiving doublet chemotherapy for aNSCLC. A reference cost (2007/08) for patient transport service of £28 per journey was used in this economic evaluation[80].

- Grade 3/4 AE management:

- The costs associated with neutropenia (£93 per AE) and febrile neutropenia (£2,286 per AE) were extracted from the ERG addendum that appraised the erlotinib NICE STA for aNSCLC[83] and the subsequent NICE erlotinib FAD[93].

- The resource use and associated costs of fatigue (£38.90 per AE), nausea and vomiting (£700.79 per AE), diarrhoea (£867.12 per AE) and anaemia (£615.04) were taken from a survey commissioned by the manufacturers of pemetrexed[70]. In this survey, four UK clinical experts provided details of the resource use required to treat these AEs. The duration of the AE and the proportion of time the patient in managed as an inpatient, outpatient and day case were then used to derive the average treatment costs.

- The cost associated with the management of rash (£117 per AE) was taken from the erlotinib NICE STA. The resource use was identified by an expert panel and includes an outpatient visit and treatment with oral tetracycline and tetracycline cream[84].

- Cost of g-CSF was estimated assuming an average BSA of 1.82$m^2$ and a daily dose of 23MU/$m^2$/day for 14 days[94].

- Best supportive care only (per cycle)

An estimate for the cost per cycle of best supportive care (£473 per cycle) was based a study reported by Clegg (2002). Case notes of 36 patients

with aNSCLC receiving terminal care were taken to derive an average BSC treatment cost, with adjustments for costs of inpatient care, outpatient care and home visits by primary care teams[68].

Patients receiving BSC (1999/00) incurred a total cost of £3,342[68] and survived for a median of 5.24 months. The total BSC cost was inflated[5] to £4,552 (2007/08). The cost per 21-day cycle for BSC was estimated to be £600 (i.e. £4,552/5.24 * 21/30.42).

- Post-progression active treatment (per cycle)

UK data on the resource use and costs for patients with aNSCLC receiving active treatment after progressing on 1st line treatment are limited.

A cost-effectiveness summary table provided in the erlotinib ERG report for the 2nd line treatment for aNSCLC estimated the total patient cost for docetaxel followed by BSC to be £12,536[79]. This cost was inflated[5] to 2007/08 to obtain a total cost of £13,369/patient.

The monthly cost of 2nd line docetaxel followed by BSC was estimated to be £1,480/month (equivalent to £1,022 per cycle) based on a mean overall survival of 9.03 months given in the ERG report.

#### 7.2.9.3 **Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?**

Resource use was not measured from the IPASS study, which was the source of evidence for the baselines and RR of disease progression. Since, IPASS was a pan-Asian study, resource use that was collected in some study centres would be unlikely to be generalisable to UK.

#### 7.2.9.4 **Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment)**.

NHS resources used to treat patients that were progression-free and following disease progression were included in the model.

#### 7.2.9.5 **What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.**

The sources of information used to value resources are described above and tabulated below:

[5] PSSRU 2008 Hospital & Community Health Services (HCHS) Pay and Price Index used to inflate the costs

**Table 29: Source of resource use and associated costs:**

| Resource | Resource use | Source of unit cost |
|---|---|---|
| Medication | Clinical trial data, SPC | BNF 57, 2009[81], NHS Dictionary of Medicines and Devices[82] |
| Delivery of chemotherapy | Clinical trial protocol, SPC | NHS reference cost (2007/08)[80] |
| EGFR test | Royal Marsden NHS Foundation Trust, Lab21 | Royal Marsden NHS Foundation Trust, Lab21 |
| Patient Monitoring | Medical opinion | NHS reference cost (2007/08)[80] |
| NHS Transport Service | ERG report[79] | NHS reference cost (2007/08)[80] |
| Management of grade 3/4 AEs | Clinician survey[70] | Pemetrexed NICE STA[70] |
| Best supportive care | Clegg et al (2002)[68] | Clegg et al (2002)[68] inflated using index from PSSRU |
| Second-line therapy | NICE recommendation[93], erlotinib NICE STA submission[84] | ERG report[79]. Inflated using the index from PSSRU. |

### 7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis?

The Single Payment Access scheme has been agreed with the Department of Health to be included in this STA submission. Gefitinib will be charged to the NHS as a single fixed payment of [redacted] per patient. The charge will be irrespective of the treatment duration but has been set at a price that offers value for money to the NHS in England and Wales. Details of the formal arrangement with the Department of Health are provided in section 10.5, Appendix 5.

Unit costs for comparators are provided in 7.2.9.2.

### 7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

Gefitinib is a targeted treatment for patient with aNSCLC that harbour somatic mutations in the EGFR gene. A positive EGFR mutation test will be a pre-requisite for patients to be treated with gefitinib.

The Royal Marsden and Lab21 are two providers who are able to provide EGFR testing for the NHS. These laboratories use the TheraScreen EGFR29 Kit to detect EGFR mutations. The test is simple to perform. After DNA extraction, real time polymerase chain reaction (PCR) assays are performed to detect the target molecule. By comparing control and mutant sample reactions users can detect and estimate low levels of mutation. No further sample processing is needed and the results can be obtained in < 3 hours. The test is highly specific and is reported to have almost 100% sensitivity (i.e. zero false negative results).

Test results can be delivered back to the multidisciplinary team to review within 5 working days of the receipt of the sample.

AstraZeneca has been working with the NHS to ensure equitable access to identifying these patients throughout England and Wales through EGFR-TK mutation testing. NHS centres already testing for the activating EGFR-TK mutation include the Royal Marsden NHS Foundation Trust (London), University Hospital of Wales (Cardiff), University Hospitals Brimingham NHS Foundation Trust (Birmingham) and the Christie NHS Foundation Trust (Manchester). A number of other NHS trusts have indicated that they have the capability to test and AstraZeneca understands that many of these will commence testing imminently. Commercial laboratories have also indicated to AstraZeneca that they have the capability to test for the mutation.

The details of the costs and sources of data for the EGFR test have been provided in 7.2.9.2

7.2.9.8 **Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?**

Resources were valued in a manner that is consistent with the reference case

7.2.9.9 **Were resource values indexed to the current price year?**

Drug acquisition costs for comparators were taken from the BNF March 2009 with the exception of generic gemcitabine whose cost was taken from the NHS Dictionary of Medicines and Devices in August 2009.

A number of diagnostic laboratories that have the capacity to provide the EGFR test have been identified at the time of submission. The Royal Marsden and Lab21 have both given prices for the current year (2009/10).

National reference costs for 2008/09 are not currently available. National reference costs for (2007/08) were used to estimate the costs associated with: the delivery of doublet chemotherapy, gefitinib patient monitoring and NHS transport services.

Post-progression costs were inflated to 2007/08 using the inflation index reported by Curtis (2008)[95]. A NHS inflation index for the current price year has not been published.

7.2.9.10 **Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.**

No additional details to add beyond those already provided.

### 7.2.10 Time preferences

**Were costs and health benefits discounted at the rates specified in NICE's reference case?**

Future costs and QALYs were both discounted at a rate of 3.5% as specified in the NICE reference case.

### 7.2.11 Sensitivity analysis

7.2.11.1 **Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.**

Structural assumptions that were investigated in the economic evaluation include:

- Treatment response: the impact of including the TrR health state in the model was examined by setting the utility increment for patients achieving a TrR to zero.
- Utility decrements of grade 3/4 AEs: the impact of including the utility decrements for grade 3/4 AEs in the model was examined by setting all the utility decrements to zero.
- Time horizon: base case 5 years was compared to time horizons of 3 years or 6 years
- Discount rate: base case 3.5% for both costs and benefits was compared to discount rates of 0% and 6%

7.2.11.2 **Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?**

One-way sensitivity analysis, using gem/carb EGFR M+ as the comparator, was conducted to systematically examine the individual effect of each of the key variables on the model output (table 30). Variables were selected that had been highlighted by the ERG in previous NICE STA submissions for aNSCLC as being of particular interest.

**Table 30: Variables and their ranges examined in one-way sensitivity analysis**

| Variable | Label | Base case | Lower Range | Upper Range | Rationale |
|---|---|---|---|---|---|
| Incidence of EGFR M+ | EGFR_inc | 16.6% | 8% | 25% | ± 50% |
| % Patients given 2nd line therapy | Prop_2ndL | 61% | 46% | 76% | ± 25% |
| % Patient given NHS transport | Prop_transp | 50% | 25% | 75% | ± 50% |
| ORR gefitinib EGFR M+ | ORR_gefM+ | 71% | 64% | 79% | Upper and lower 95% CI elicited from IPASS |

| Variable | Label | Base case | Lower Range | Upper Range | Rationale |
|---|---|---|---|---|---|
| ORR gem/carb | ORR_gc | 43% | 37% | 50% | Upper and lower limit of 95% CrI* from MTC |
| HR PFS gefitinib EGFR M+ | HR_PFS_gef | 0.43 | 0.34 | 0.53 | Upper and lower limit of 95% CI from meta-analysis |
| HR OS gefitinib EGFR M+ | HR_PFS_gef | | | | Upper and lower limit of 95% CI from IPASS |
| HR PFS gem/carb | HR_PFS_gc | 1.23 | 0.68 | 2.06 | Upper and lower 95% CrI* from MTC |
| HR OS gem/carb | HR_OS_gc | 0.95 | 0.73 | 1.23 | Upper and lower 95% CrI* from MTC |
| Max number of cycles chemotherapy | Max_cyc_gc | 6 | 4 | 8 | ± 2 cycles |
| Incidence of grade 3/4 febrile neutropenia for gem/carb | Inc_FN_gc | 1.0% | 0.5% | 1.5% | ± 50% |
| Incidence of grade 3/4 diarrhoea with gefitinib | Inc_diarr | 5.3% | 2.7% | 8.0% | ± 50% |
| Incidence of grade 3/4 rash with gefitinib | Inc_rash | 2.3% | 1.2% | 3.5% | ± 50% |
| Utility increment responders | Ut_resp | 0.0193 | 0.0065 | 0.0321 | Upper and lower 95% CI |
| Utility decrement post-progression | Ut_prog | 0.1798 | 0.1373 | 0.2223 | Upper and lower 95% CI |
| Utility decrement oral therapy | Ut_oral | 0.0139 | 0.0000 | 0.0367 | Upper and lower 95% CI |
| Utility decrement iv therapy | Ut_iv | 0.0425 | 0.0032 | 0.0818 | Upper and lower 95% CI |
| Cost gem/carb per cycle | Cst_gc | £999 | £501 | £999 | - 50% |
| Cost gem/carb administration | Cst_admin | £307 | £154 | £461 | ± 50% |
| Cost EGFR test for gefitinib treated patients | Cst_EGFR | [redacted] | [redacted] | [redacted] | Lab21 commercial contract |
| Cost Best Supportive Care (BSC) per cycle | Cst_BSC | £600 | £300 | £900 | ± 50% |
| Cost 2nd line therapy followed by BSC per cycle | Cst_2ndL | £1,022 | £511 | £1,533 | ± 50% |
| Cost grade 3/4 febrile neutropenia | Cst_FN | £2,286 | £1,143 | £3,429 | ± 50% |
| Cost grade 3/4 diarrhoea | Cst_diarr | £867 | £434 | £1,301 | ± 50% |
| Cost grade 3/4 rash | Cst_rash | £117 | £58 | £175 | ± 50% |
| Cost g-CSF (per patient) | Cst_gCSF | £1,284 | £642 | £1,926 | ± 50% |

* CrI = credible interval

### 7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources

**should be clearly stated; including the derivation and value of 'priors'.**

Probabilistic sensitivity analysis (PSA) was undertaken in the economic evaluation to assess the uncertainty in the model outputs. Uncertainty around the Weibull scale (λ) and shape (α) parameters that define the progression free and overall survival functions was modeled using a normal distribution of the covariates. The distributions and sources of the other variables that were included in the PSA are given in table 31.

**Table 31: PSA variables, distributions and their source**

| Variable | Base case | Range | | Distribution | Source |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| EGFR mutation rate | 16.6% | 15% | 18% | Beta | Rosell (2009)[76] |
| ORR gefitinib EGFR M+ | 71% | 64% | 79% | Beta | IPASS |
| ORR gem/carb EGFR M+ | 43% | 37% | 50% | Beta | MTC |
| ORR pac/carb EGFR M+ | 47% | 39% | 56% | Beta | IPASS |
| ORR vin/cis EGFR M+ | 50% | 45% | 54% | Beta | MTC |
| ORR gem/cis EGFR M+ | 51% | 46% | 56% | Beta | MTC |
| HR PFS gefitinib EGFR M+ | 0.43 | 0.34 | 0.53 | Gamma | Meta-analysis |
| HR PFS gem/carb EGFR M+ | 1.23 | 0.68 | 2.06 | Gamma | MTC |
| HR PFS vin/cis EGFR M+ | 0.99 | 0.80 | 1.21 | Gamma | MTC |
| HR PFS gem/cis EGFR M+ | 0.92 | 0.81 | 1.05 | Gamma | MTC |
| HR OS gefitinib EGFR M+ | 0.78 | 0.50 | 1.20 | Gamma | IPASS |
| HR OS gem/carb EGFR M+ | 0.95 | 0.73 | 1.23 | Gamma | MTC |
| HR OS vin/cis EGFR M+ | 1.08 | 0.90 | 1.28 | Gamma | MTC |
| HR OS gem/cis EGFR M+ | 0.92 | 0.81 | 1.04 | Gamma | MTC |
| Baseline utility | 0.6532 | 0.6096 | 0.6968 | Beta | Nafees (2008)[78] |
| Response (utility increment) | 0.0193 | 0.0068 | 0.0321 | Beta | Nafees (2008) [78] |
| Utility decrements | | | | | |
| - Disease progression | 0.1798 | 0.1372 | 0.2168 | Beta | Nafees (2008)[78] |
| - Grade 3/4 neutropenia | 0.0897 | 0.0595 | 0.1200 | Beta | Nafees (2008) [78] |
| - Grade 3/4 febrile neutropenia | 0.0900 | 0.0580 | 0.1220 | Beta | Nafees (2008) [78] |
| - Grade 3/4 fatigue | 0.0743 | 0.0372 | 0.1097 | Beta | Nafees (2008) [78] |
| - Grade 3/4 nausea & vomiting | 0.0480 | 0.0162 | 0.0797 | Beta | Nafees (2008) [78] |
| - Grade 3/4 diarrhoea | 0.0466 | 0.0161 | 0.0770 | Beta | Nafees (2008) [78] |
| - Hair loss (partial or complete) | 0.0450 | 0.0160 | 0.0740 | Beta | Nafees (2008) [78] |
| - Grade 3/4 rash | 0.0325 | 0.0095 | 0.0555 | Beta | Nafees (2008) [78] |
| - Grade 3/4 anaemia | 0.0743 | 0.0372 | 0.1097 | Beta | Eli Lilly (2009)[70] |
| - Intravenous therapy | 0.0425 | 0.0033 | 0.0817 | Beta | ERG (2006)[79] |
| - Oral therapy | 0.0139 | 0.0089 | 0.0367 | Beta | ERG (2006)[79] |

| Variable | Base case | Range | | Distribution | Source |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| Cost of EGFR testing | [redacted] | [redacted] | [redacted] | Gamma | Lab21 |
| Cost of gem/carb admin (per cycle)* | £307 | £172 | £488 | Gamma | Reference costs[80] |
| Cost of pac/carb admin (per cycle)* | £153 | £89 | £280 | Gamma | Reference costs[80] |
| Cost of vin/cis admin (per cycle)* | £527 | £349 | £683 | Gamma | Reference costs[80] |
| NHS transport service (per journey)* | £28 | £20 | £34 | Gamma | Reference costs[80] |
| Patient monitoring (per visit) | £86 | £57 | £110 | Gamma | Reference costs[80] |

* Inter-quartile range given in the Reference Costs was used as an estimate of the variability in the point estimate for the chemotherapy administration costs

### 7.2.12 Statistical analysis

#### 7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

A Weibull regression model using patient level data from IPASS was used to derive probabilities for progression-free, post-progression and death for the interventions of interest to the NICE decision problem. This type of model has been extensively used for survival data, because it fits many survival data well and has a relatively simple survival function:

$S(t) = \exp[-\lambda t^{\alpha}]$ for $t > 0$; $\alpha, \lambda > 0$ where $S(t)$ is survival at time t, $\lambda$ is the scale parameter and $\alpha$ the shape parameter ($\alpha < 1$ corresponds to a decreasing hazard).

Covariates included in the Weibull model were: mutation status, gender, performance status and smoking history.

The gefitinib EGFR M+ HR for PFS, 0.43 (95% CrI: 0.34,0.53), that was obtained from the meta-analysis (see section 6.5), was applied to the PFS Weibull survival function for pac/carb EGFR M+ to estimate the probability of patients treated with gefitinib remaining progression-free at each cycle of the model:

$$S(t)_{\text{PFS gef EGFR M+}} = \exp[-HR_{(\text{PFS gef EGFR M+})} * \lambda_{\text{PFS pac/carbEGFR M+}} * t^{\alpha \text{PFS pac/carb EGFR M+}}]$$

Similarly, the OS HR for gefitinib EGFR M+ reported in IPASS (0.78, 95% CI: 0.50 to 1.20) was applied to the WB regression function for OS for pac/carb EGFR M+ to estimate the probability of these remaining alive at each cycle of the model.

PFS and OS HRs for the indirect comparators that were reported in MTC (see section 6.6) were applied to the corresponding Weibull survival functions for pac/carb EGFR M+, as outlined above, to estimate the respective transition probabilities.

7.2.12.2 **Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.**

Transition probabilities for disease progression and death do vary over time for patients with aNSCLC. The Weibull regression model that has been used in this economic evaluation is able to capture the variation in the probabilities of these events occurring over time.

### 7.2.13 Validity

**Describe the measures that have been undertaken in order to validate and check the model.**

The following measures were taken to check and validate the integrity of the model:

1. A health economist, employed by AstraZeneca UK, who was not directly involved in the submission, conducted internal validity checks on the calculations and formulae used in the model.

2. An advisory panel consisting of two independent health economists from academia and two consultants who specialise in the treatment of lung cancer was commissioned to critique the structure of the model, the key assumptions and data inputs.

3. The clinical output generated by the model was compared to the results observed in IPASS (table 32). On inspection, the degree of error between the fitted and empirical curves was considered acceptable.

**Table 32 Model output versus IPASS trial outcomes (EGFR M+ population)**

| Outcome | Gefitinib Model Results | | IPASS Results | |
|---|---|---|---|---|
| | Gefitinib | Pac/carb | Gefitinib | Pac/carb |
| Median PFS (months) | 9.2 | 6.2 | 9.5 | 6.3 |
| 4 months PFS (%) | 88.3% | 77.2% | 81.6% | 80.5% |
| 6 months PFS 9%) | 75.3% | 55.4% | 70.1% | 51.1% |
| 12 months PFS (%) | 34.6% | 11.0% | 36.9% | 9.1% |
| Median OS (months) | 23.7 | 20.5 | NA | 19.5 |
| 6 month OS (%) | 94.8% | 93.4% | 95.4% | 95.3% |
| 9 month OS (%) | 89.2% | 86.4% | 87.8% | 86.9% |
| 12 months OS (%) | 82.4% | 78.0% | 80.7% | 75.9% |

NA = not available. Overall survival data are not mature. A final analysis of OS is expected in Q2 2010.

4. The mean total days for the pac/carb EGFR M+ population estimated by the model (109 days equivalent to 5.2 cycles) was compared and found to be in good agreement to the mean total days of treatment reported in IPASS (108 days)[71]. The model results were also in reasonable agreement with market research data [96]commissioned by

the manufacturer that reported a mean number of gem/carb treatment cycles delivered in 1st line NSCLC in England and Wales of 4.8 (model estimate was 5.1 for EGFR M+ patients treated with gem/carb).

5. A meta-analysis (Johnson 2006)[97] has reported a weak but positive correlation between PFS (and tumour response) and OS in patients with aNSCLC. The authors reported that in lung cancer trials, to predict a difference in OS an incremental gain in median PFS of 1.8 months was required for trials with 750 patients. For tumour response, a difference of 18% was required for trials with 750 patients. In IPASS, the median PFS and ORR benefit observed in EGFR M+ patient treated with gefitinib compared to pac/carb was well in excess of these threshold effect sizes (see section 6.4) which adds weight to the OS outcomes predicted by the gefitinib economic model.

## *7.3 Results*

### 7.3.1 Base-case analysis

#### 7.3.1.1 What were the results of the base-case analysis?

In the deterministic analysis, the use of gefitinib in EGFR M+ patients with aNSCLC versus gem/carb EGFR M+ was associated an additional 4.7 months mean PFS (10.7 months versus 6.1 months, respectively) (table 32). The OS survival advantage of gefitinib EGFR M+ versus gem/carb EGFR M+ was estimated to be 2.7 months (25.9 months versus 23.2 months, respectively) (table 33).

One year PFS and OS estimates suggest that for every 1,000 patients treated, 310 more EGFR M+ patients treated with gefitinib are likely to be progression-free and 36 more patients alive at 12 months compared to those receiving gem/carb (table 33).

In terms of overall health care costs, gefitinib EGFR M+ was associated with an incremental cost of £[redacted] versus gem/carb EGFR M+.

With the exception of the SPA price ([redacted] per patient), the costs associated with EGFR testing ([redacted]) were the largest component of the progression-free health care costs (table 34) for the gefitinib treated patients.

Drug costs (£5,047 per patient) and the costs associated with chemotherapy administration and monitoring (£1,738 per patient) were the largest pre-progression healthcare costs for patients receiving gem/carb.

The ICER for gefitinib EGFR M+ versus gem/carb EGFR M+ was £20,744/QALY (table 35).

The ICERs for gefitinib EGFR M+ versus the other comparators included in the submission were: £19,402/QALY (pac/carb EGFR M+), £35,992/QALY (vin/cis EGFR M+) and £28,633/QALY (gem/cis) (table 35).

**Table 33: Markov model results for base case analysis (discounted)**

| | Mean PFS (mths) | Mean OS (mths) | 1 Year PFS (%) | 1 Year OS (%) | Mean Costs | Mean QALYs |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Gefitinib EGFR M+ | 10.7 | 25.9 | 36.8% | 81.5% | £[redacted] | 1.111 |
| Gem/carb EGFR M+ | 6.1 | 23.2 | 5.8% | 78.0% | £27,873 | 0.934 |
| Pac/carb EGFR M+ | 6.8 | 22.6 | 9.8% | 76.9% | £27,902 | 0.923 |
| Vin/cis EGFR M+ | 6.8 | 21.6 | 10.0% | 75.3% | £23,516 | 0.888 |
| Gem/cis EGFR M+ | 7.1 | 23.6 | 11.8% | 78.6% | £27,401 | 0.966 |

**Table 34: Disaggregated mean costs for base case analysis (discounted)**

| | **Gefitinib EGFR M+** | **Gem/carb EGFR M+** | **Pac/carb EGFR M+** | **Vin/cis EGFR M+** | **Gem/cis EGFR M+** |
|---|---|---|---|---|---|
| **Pre-progression** | | | | | |
| - Drugs | [redacted] | £5,047 | £7,748 | £2,101 | £4,158 |
| - EGFR testing | [redacted] | - | - | - | - |
| - Admin and monitoring | £874 | £1,738 | £1,034 | £2,987 | £3,032 |
| - NHS funded transport | - | £283 | £146 | £292 | £295 |
| - AE management | £58 | £458 | £218 | £483 | £350 |
| - g-CSF prophylaxis | - | £278 | £278 | £278 | £278 |
| **Post-progression** | | | | | |
| - Post-progression active treatment | £12,641 | £14,595 | £13,439 | £12,634 | £14,019 |
| - BSC | £4,742 | £5,475 | £5,040 | £4,740 | £5,259 |
| **Total** | **£[redacted]** | **£27,873** | **£27,902** | **£23,516** | **£27,401** |
| **Mean # cycles** | NA | 5.1 | 5.2 | 5.2 | 5.3 |

**Table 35: Pairwise incremental results for the base case analysis (discounted)**

| | Δ mean PFS (mths) | Δ mean OS (mths) | Δ 1 Yr PFS (%) | Δ 1 Yr OS (%) | Δ mean Costs | Δ mean QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Gefitinib EGFR M+ | - | - | - | | - | - | - |
| Gem/carb EGFR M+ | 4.7 | 2.7 | 31.0% | 3.6% | £3,666 | 0.177 | **£20,744** |
| Pac/carb EGFR M+ | 3.9 | 3.3 | 27.0% | 4.6% | £3,637 | 0.187 | **£19,402** |
| Vin/cis EGFR M+ | 3.9 | 4.2 | 26.7% | 6.2% | £8,024 | 0.223 | **£35,992** |
| Gem/cis EGFR M+ | 3.6 | 2.2 | 25.0% | 2.9% | £4,138 | 0.145 | **£28,633** |

### 7.3.2 Subgroup analysis

#### 7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

The results of the subgroup analyses are presented in tables 36 to 38.

**Table 36: Pairwise incremental results: adenocarcinoma versus non-adenocarcinoma**

| | Adenocarcinoma (EGFR M+ 16%) | | | Non-adenocarcinoma (EGFR M+ 3%) | | |
|---|---|---|---|---|---|---|
| | Δ mean Costs | Δ mean QALYs | ICER (£/QALY) | Δ mean Costs | Δ mean QALYs | ICER (£/QALY) |
| Gefitinib EGFR M+ *vs* | - | - | - | - | - | - |
| Gem/carb EGFR M+ | £3,704 | 0.177 | **£20,961** | £8,309 | 0.177 | **£47,015** |
| Pac/carb EGFR M+ | £3,675 | 0.187 | **£19,607** | £8,279 | 0.187 | **£44,169** |
| Vin/cis EGFR M+ | £8,062 | 0.223 | **£36,164** | £12,666 | 0.223 | **£56,816** |
| Gem/cis EGFR M+ | £4,176 | 0.145 | **£28,899** | £8,870 | 0.145 | **£60,759** |

**Table 37: Pairwise incremental results: female versus male**

| | Female (EGFR-TK M+ 17%) | | | Male (EGFR-TK M+ 6%) | | |
|---|---|---|---|---|---|---|
| | **Δ mean Costs** | **Δ mean QALYs** | **ICER (£/QALY)** | **Δ mean Costs** | **Δ mean QALYs** | **ICER (£/QALY)** |
| Gefitinib EGFR M+ *vs* | - | - | - | - | - | - |
| Gem/carb EGFR M+ | £3,642 | 0.177 | **£20,608** | £5,475 | 0.177 | **£30,982** |
| Pac/carb EGFR M+ | £3,613 | 0.187 | **£19,273** | £5,446 | 0.187 | **£29,054** |
| Vin/cis EGFR M+ | £8,000 | 0.223 | **£35,883** | £9,833 | 0.223 | **£44,107** |
| Gem/cis EGFR M+ | £4,114 | 0.145 | **£28,467** | £5,947 | 0.145 | **£41,153** |

**Table 38: Pairwise incremental results: never smokers versus ever smokers**

| | Never smokers (EGFR M+ 40%) | | | Ever smokers (EGFR M+ 7%) | | |
|---|---|---|---|---|---|---|
| | **Δ mean Costs** | **Δ mean QALYs** | **ICER (£/QALY)** | **Δ mean Costs** | **Δ mean QALYs** | **ICER (£/QALY)** |
| Gefitinib EGFR M+ *vs* | - | - | - | - | - | - |
| Gem/carb EGFR M+ | £3,067 | 0.177 | **£17,354** | £5,070 | 0.177 | **£28,692** |
| Pac/carb EGFR M+ | £3,038 | 0.187 | **£16,206** | £5,041 | 0.187 | **£26,895** |
| Vin/cis EGFR M+ | £7,425 | 0.223 | **£33,304** | £9,428 | 0.223 | **£42,291** |
| Gem/cis EGFR M+ | £3,539 | 0.145 | **£24,488** | £5,542 | 0.145 | **£38,352** |

### 7.3.3 Sensitivity analyses

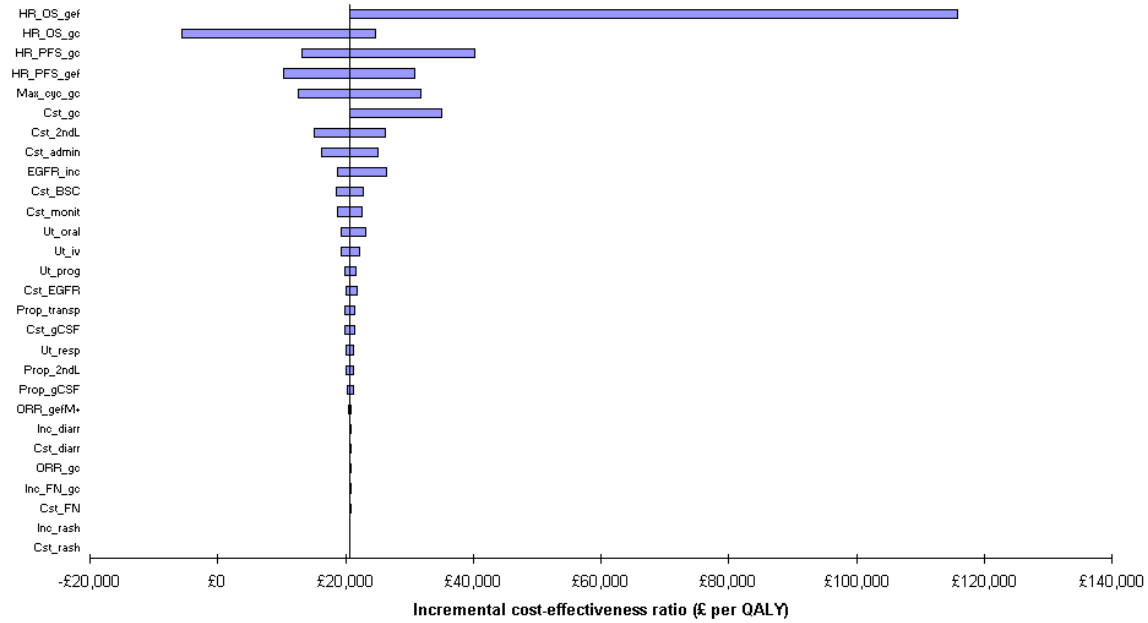
#### 7.3.3.1 What were the main findings of the sensitivity analyses?

**One-way sensitivity analysis**

The model output was found to be sensitive to a number of the key model parameters (see figure 26). The five main key drivers of the cost-effectiveness results that were identified in the one-way sensitivity analysis were:

- OS HR for gem/carb EGFR M+ [HR_OS_gef]: ± 95% CI from the base case gave an ICER range of £25,638/QALY to £115,884/QALY (Δcost = -£2,411, ΔQALYs = -0.0208)
- OS HR for gem/carb EGFR M+ [HR_OS_gc]: ± 95% CrI from the base case gave an ICER range of -£5,655/QALY (Δcost = -£262, ΔQALYs = 0.0471) to £24,716/QALY
- PFS HR for gem/carb EGFR M+ [HR_PFS_gc]: ± 95% CrI from the base case gave an ICER range of £13,246/QALY to £40,313/QALY
- PFS HR for gefitinib EGFR M+ [HR_PFS_gef]: ± 95% CI from the base case gave an ICER range of £10,386/QALY to £30,825/QALY
- Maximum number of chemotherapy cycles [Max_cyc_gc]: varied from 4 to 8 gave an ICER range of £12,552/QALY to £31,704/QALY.

**Figure 26: Tornado diagram of base case analysis (gefitinib EGFR M+ vs gem/carb EGFR M+)**




The one-way sensitivity analysis accessing the impact of varying the maximum number of chemotherapy cycles focuses on the cost component of the cost-effectiveness calculation. However, there is still some debate on the optimal duration of 1st line chemotherapy in aNSCLC. There is some evidence that extending third-generation chemotherapy beyond 4 cycles substantially improves PFS (and to a lesser extent OS)[98,99]. This effect has not been captured in the one-way sensitivity analysis, which only takes into account the change in the cost element of the ICER when the maximum number of cycles is varied and not differences in treatment benefit.

**Scenario Analyses**

a) Treatment response (TrR): the exclusion of a TrR health state in which patients responding to treatment gained a higher utility value than those with

stable disease decreased the incremental QALY gain by 0.008 QALYs (equivalent to 2.9 days of perfect health). The ICER increased from £20,744/QALY to £21,690/QALY (see table 39).

**Table 39: Impact of treatment response health state on base case results (gefitinib EGFR M+ vs gem/carb EGFR M+)**

| | **TrR health state included (base case)** | | **TrR health state excluded** | |
|---|---|---|---|---|
| | **Δ mean QALYs** | **ICER** | **Δ mean QALYs** | **ICER** |
| Gefitinib EGFR M+ *vs* gem/carb EGRG M+ | 0.177 | **£20,744/QALY** | 0.169 | **£21,690/QALY** |

b) Utility decrement of grade 3/4 AEs: removing the utility decrements associated with grade 3/4 AEs from the model would not had little impact on the cost-effectiveness results (table 40). The incremental QALY gain decreased by 0.006 QALYs (equivalent to 2.2 days of perfect health), which led to an increase in the ICER from £20,744/QALY to £21,329/QALY.

**Table 40: Impact of treatment response health state on base case results (gefitinib EGFR M+ vs gem/carb EGFR M+)**

| | **Utility decrements for grade 3/4 AEs included (base case)** | | **Utility decrements for grade 3/4 AEs excluded** | |
|---|---|---|---|---|
| | **Δ mean QALYs** | **ICER** | **Δ mean QALYs** | **ICER** |
| Gefitinib EGFR M+ *vs* gem/carb EGRG M+ | 0.177 | **£20,744/QALY** | 0.171 | **£21,329/QALY** |

c) Time horizon: reducing the base case time horizon of the analysis from 5 years to 3 years had little effect on the incremental QALYs but decreased the incremental costs from £3,666 to £2,721. The ICER for the 3-year time horizon was £15,398/QALY (see table 41).

Adopting a 6-year time horizon had little effect on the base case results (see table 41).

**Table 41: Impact of time horizon on base case results (gefitinib EGFR M+ vs gem/carb EGFR M+)**

| | **Δ mean PFS (months)** | **Δ mean OS (months)** | **Δ mean Costs** | **Δ mean QALYs** | **ICER (£/QALY)** |
|---|---|---|---|---|---|
| 5 years (base case) | 4.7 | 2.7 | £3,666 | 0.177 | **£20,744** |
| 3 years | 4.7 | 2.7 | £2,721 | 0.177 | **£15,398** |
| 6 years | 4.7 | 2.7 | £3,761 | 0.177 | **£21,284** |

d) Discount rate: changing from the base case discount rate of 3.5% for both costs and QALYs to 0% for both costs and QALYs had little effect on the model output (table 42). The mean incremental costs were increased from £3,666 to £3,722 and the mean incremental QALY gain increased from 0.177 to 0.188. The ICER decreased from £20,744/QALY to £19,815/QALY.

Conversely, adopting a 6% discount rate for both costs and QALYs increased the ICER from £20,744/QALY to £21,454/QALY.

**Table 42: Impact of varying the discount rate on base case results (gefitinib EGFR M+ vs gem/carb EGFR M+)**

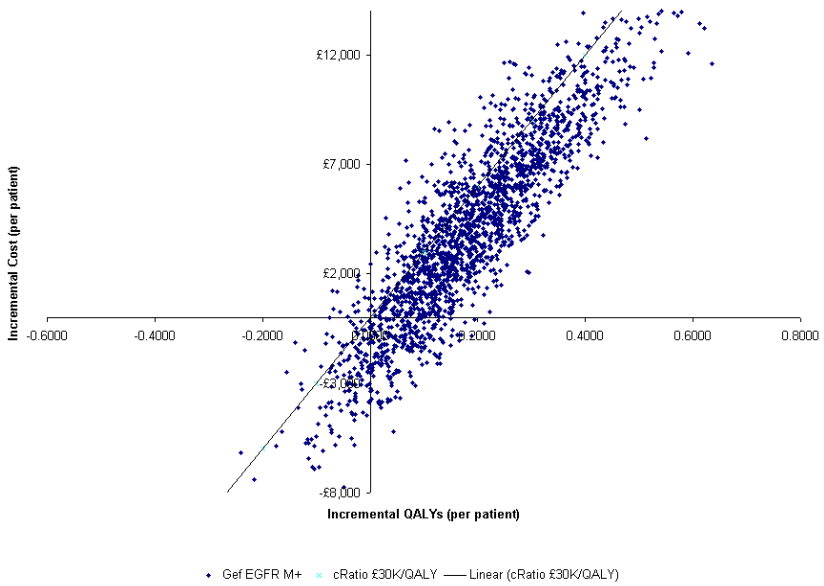
| | **Δ mean PFS (months)** | **Δ mean OS (months)** | **Δ mean Costs** | **Δ mean QALYs** | **ICER (£/QALY)** |
|---|---|---|---|---|---|
| 3.5% discount for both costs and QALYs (base case) | 4.7 | 2.7 | £3,666 | 0.177 | **£20,744** |
| 0% discount for both costs and QALYs | 4.7 | 2.7 | £3,722 | 0.188 | **£19,815** |
| 6% discount for both costs and QALYs | 4.7 | 2.7 | £3,639 | 0.170 | **£21,454** |

**Probabilistic sensitivity analysis**

A scatterplot for the base case analysis of the use gefitinib in EGFR M+ patients with aNSCLC *versus* gem/carb in an EGFR M+ confirmed population is presented in figure 27.

At a willingness to pay threshold (WTP) of £20K/QALY there was a 43% probability of gefitinib EGFR M+ being a cost-effective versus gem/carb EGFR M+. This increased to 83% at a WTP threshold of £30K/QALY.

**Figure 27: Scatterplot of gefitinib EGFR M+ *versus* gem/carb EGFR M+**




The cost-effectiveness acceptability curve (CEAC) for gefitinib EGFR M+ versus doublet chemotherapy EGFR M+ is presented in figure 28.

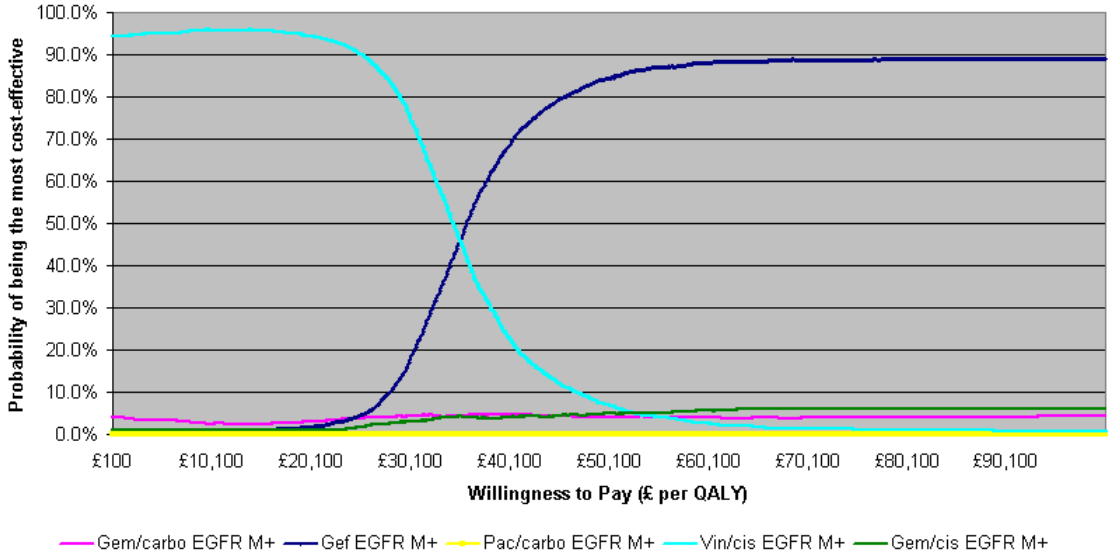
Given the constraints of the available clinical and utility data, vinorelbine/cisplatin, the combination with the lowest drug acquisition costs, was found to be the most cost-effective treatment for the 1st line treatment of EGFR M+ patients up to a WTP threshold of £35,100/QALY. Beyond this threshold, gefitinib EGFR M+ becomes the most cost-effective treatment option.

At a WTP threshold of £30K/QALY, the probabilities of being the most cost-effective treatment option for the NHS were, in descending order, vin/cis EGFR M+ (75%), gefitinib EGFR M+ (18%), gem/carb EGFR M+ (4%), gem/cis EGFR M+ (3%) and pac/carb EGFR M+ (0%).

The mean ICER for gefitinib EGFR M+ versus doublet chemotherapy EGFR M+ was £35,700/QALY.

The probability of gemcitabine containing doublet chemotherapy being the most cost-effective treatment option for the treatment of EGFR M+ patients with aNSCLC, at any given WTP threshold, was less than 10%.

**Figure 28: CEAC gefitinib EGFRM+ *versus* doublet chemotherapy (EGFR M+ pop)**




7.3.3.2 **What are the key drivers of the cost effectiveness results?**

See answer to question 7.3.3.1

### 7.3.4 Interpretation of economic evidence

7.3.4.1 **Are the results from this economic evaluation consistent with the published economic literature?**

The systematic review that was conducted for this submission (see 7.1.1) failed to identify any studies in the published economic literature that have assessed the cost-effectiveness of gefitinib EGFR M+ as a 1st line treatment for aNSCLC.

7.3.4.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology?**

Yes, the economic evaluation is relevant to all patients with aNSCLC that are eligible for 1st line doublet chemotherapy and harbour EGFR-TK mutations.

7.3.4.3 **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

The main strengths of the cost-utility analysis are outlined below:

- At a WTP threshold of £30K/QALY, gefitinib EGFR M+ was found to be cost-effective compared to gem/carb EGFR M+, the most widely used 1st line doublet chemotherapy for aNSCLC in the UK. Ranges of sensitivity analyses were undertaken that confirmed that the base case results were robust.

- The economic model was based on the results of a large, phase III randomised trial that directly compared gefitinib to paclitaxel plus

carboplatin in chemotherapy naïve patients with aNSCLC[9]. Paclitaxel plus carboplatin was identified by NICE as a comparator of interest in the scoping exercise.

- NICE guidance for undertaking systematic reviews and indirect comparisons were applied throughout the review.

- Validation checks on the model have shown that it is able to reproduce the clinical outcomes of IPASS with an acceptable degree of precision.

The weaknesses of the evaluation are:

- The IPASS study population is not readily generalisable to patients observed in routine clinical practice in the UK. IPASS was conducted in a predominantly female population with adenocarcinoma who had never smoked and took place in study centres in Asia. However, there is no biological rationale to support the contention that response to gefitinib may differ between an EGFR M+ Asian patient and an EGFR M+ Caucasian patient. Although the prevalence of the mutation is lower in the UK, the clinical characteristics and histological types of tumour associated with somatic EGFR mutation are the same regardless of geography. Nor is there any difference in the pharmacokinetic profile according to ethnicity.

- EGFR testing is not routinely conducted in the UK. The incidence of EGFR mutations in the UK patient population with aNSCLC and the cost of EGFR testing to the NHS are areas of uncertainty. If healthcare professionals were to pre-select patients for EGFR testing based on clinical characteristics, the cost associated with identifying patients eligible for gefitinib would be markedly reduced. Similarly, the cost of the test itself is anticipated to fall in subsequent years as EGFR testing is adopted into the treatment pathway for lung cancer. Both factors would improve the cost-effectiveness of gefitinib versus doublet chemotherapy.

- EQ-5D was not used to estimate changes in HRQoL in IPASS. Utility estimates for the 1st line treatment of aNSCLC were sourced from a study of the 2nd line treatment of aNSCLC. However, it should be noted that one-way sensitivity analysis suggests that the utility values have little impact on the overall results of the analysis.

#### 7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

No further analyses have been identified

## 8 Assessment of factors relevant to the NHS and other parties

### 8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales, in the first five years following the introduction of gefitinib for the 1st line

treatment of aNSCLC in EGFR M+ patients is presented in table 43. The net estimated annual budget impact for the NHS in England & Wales in 2010/11 is £[redacted] rising to £[redacted]. in 2014/15.

**Table 43 Estimated annual budget impact of gefitinib in England & Wales (2010 to 2015)**

| | Year of Introduction | | | | |
|---|---|---|---|---|---|
| | **2010/11** | **2011/12** | **2012/13** | **2013/14** | **2014/15** |
| # Gefitinib treated patients | 290 | 304 | 319 | 335 | 352 |
| **Gefitinib treatment costs** | | | | | |
| - Gefitinib Single Fixed Price | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - EGFR Test | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - Patient monitoring | £253,429 | £262,663 | £278,772 | £292,754 | £307,610 |
| - NHS funded transport for chemotherapy | NA | NA | NA | NA | NA |
| - CTC grade 3/4 management | £16,749 | £17,558 | £18,424 | £19,348 | £20,330 |
| - g-CSF for neutropenia prophylaxis | NA | NA | NA | NA | NA |
| **Total Costs** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| # Doublet chemotherapy treated patients (i.e. no gefitinib pts) | 290 | 304 | 319 | 335 | 352 |
| **Doublet chemotherapy costs** | | | | | |
| - Drug costs | £1,405,181 | £1,473,017 | £1,545,699 | £1,623,226 | £1,705,598 |
| - EGFR Test | NA | NA | NA | NA | NA |
| - Chemotherapy delivery/patient monitoring | £547,775 | £574,219 | £602,552 | £632,774 | £664,885 |
| - NHS funded transport for chemotherapy | £80,732 | £84,629 | £88,805 | £93,259 | £97,992 |
| - CTC grade 3/4 management | £128,825 | £135,044 | £141,707 | £148,815 | £156,367 |
| - g-CSF for neutropenia prophylaxis | £80,483 | £84,368 | £88,531 | £92,972 | £97,690 |
| **Total Costs** | **£2,162,512** | **£2,266,909** | **£2,378,763** | **£2,498,074** | **£2,624,842** |
| **Net budget impact** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

## 8.2 What number of patients were assumed to be eligible? How was this figure derived?

It is estimated that there will be **290** EGFR M+ patients with aNSCLC eligible for treatment with gefitinib in 2010/11 increasing to **352** patients in 2014/15 (see table 44).

These figures were derived as follows:

- There were a total of **33,410** registrations for lung cancer in England[100] & Wales[101] in 2006 (31,127 in England and 2,283 Wales). Cancer registration data beyond this time point were unavailable. The

incidence of lung cancer is assumed to remain constant over the next 5 years.

- NSCLC accounts for 80% to 85% of lung cancer cases[3]. There are an estimated **26,728** cases of NSCLC in England and Wales if an incidence of 80% is assumed.

- In cases where a tissue diagnosis of NSCLC is confirmed, staging may be possible for around 68% of patients (**18,175** of the 26,728 cases of NSCLC). Approximately 80% of these patients will have locally advanced or metastatic (stage IIIA/IV) disease (**14,540** out of 18,175)[102].

- In 2005, NICE estimated that approximately 30% of patients with aNSCLC would be eligible for chemotherapy[3]. Based on this estimate, the number of aNSCLC patients in England & Wales that would be eligible for chemotherapy is **4,362** out of 14,540. It is assumed the proportion of patients eligible for chemotherapy will remain constant over the next 5 years.

- Despite 85% of patients in IPASS consenting to provide tissue sample for biomarker analysis, due to a lack of available and/or suitable sample, evaluable EGFR mutation status results were only obtained for 40% of patients. If this finding is replicated in England and Wales, EGFR mutation tests will be conducted and results available for **1,745** patients.

- It is assumed that improvements in tissue sample collection and EGFR testing (including detecting EGFR mutation in blood samples of patients with aNSCLC) will increase the EGFR detection rate by 5% each year. By the year 2014/2015, it is anticipated that EGFR mutation status will be available for around 60% of patients diagnosed with aNSCLC.

- Positive EGFR mutation status has been estimated to be 16.6% in the European population[76]. Given this figure, it is estimated that there will be **290** EGFR M+ patients with aNSCLC in England & Wales that would be eligible for gefitinib. It is assumed that there will be no change in the incidence of EGFR mutation in England and Wales over the next 5-years.

**Table 44: Estimated number of EGFR M+ patients with aNSCLC eligible for gefitinib in England & Wales**

| Assumption | Year from Introduction | | | | |
|---|---|---|---|---|---|
| | 2010/11 | 2011/12 | 2012/13 | 2013/14 | 2014/15 |
| # Patients with confirmed aNSCLC | 14,540 | 14,540 | 14,540 | 14,540 | 14,540 |
| # Patients with aNSCLC eligible for chemotherapy | 4,362 | 4,362 | 4,362 | 4,362 | 4,362 |

| Assumption | Year from Introduction | | | | |
|---|---|---|---|---|---|
| | 2010/11 | 2011/12 | 2012/13 | 2013/14 | 2014/15 |
| # Patients with aNSCLC eligible for chemotherapy with known EGFR mutation status | 1,745 | 1,832 | 1923 | 2020 | 2121 |
| # EGFR M+ patients with aNSCLC eligible for treatment with gefitinib | 290 | 304 | 319 | 335 | 352 |

### 8.3 What assumption(s) were made about current treatment options and uptake of technologies?

Platinum based doublet chemotherapy is the current standard of care for patients diagnosed with aNSCLC who are suitable for anti-cancer therapy[3]. Gemcitabine plus carboplatin is the most widely used doublet chemotherapy in the United Kingdom accounting for around 81% of all doublet chemotherapy regimens[10]. Other doublet chemotherapy regimens that are used include: paclitaxel (or docetaxel) plus carboplatin (4%), vinorelbine plus cisplatin (9%) and gemcitabine plus cisplatin (5%)[10]. Weighted average costs based on doublet chemotherapy usage in the UK have been used in the budget impact calculations.

### 8.4 What assumption(s) were made about market share (where relevant)?

Gefitinib is currently the only EGFR-TKI that is licensed in England and Wales as a 1st line treatment for aNSCLC for patients who are EGFR M+. It is assumed that in the first year of introduction every EGFR M+ patient with aNSCLC, who would otherwise receive doublet chemotherapy, will be treated with gefitinib. However, in subsequent years more 1st line treatment options, including pemetrexed and erlotinib, are likely to become available for patients with aNSCLC who would otherwise be eligible for gefitinib. The uptake of these alternative therapies and their impact on the gefitinib market share is uncertain and not possible to quantify in the budget impact analysis

### 8.5 What unit costs were assumed? How were these calculated?

The Single Payment Access scheme has been agreed with the Department of Health to be included in this STA submission. Gefitinib will be charged to the NHS as a single fixed payment of [redacted] per patient. In addition, EGFR testing costs of [redacted] have been assumed for gefitinib that is based on a unit test cost of [redacted] and an incidence of EGFR mutation of 16.6% in England and Wales. It has been assumed that a consultant will review gefitinib treated patients on a monthly basis at a cost of £86[80] per visit until disease progression. It is also assumed that an average cost of £60 per person will be required to manage treatment related AEs.

Costs for doublet chemotherapy are based on an average BSA of 1.82m$^2$ and an average of 5 treatment cycles. Drug acquisition costs (per cycle) for gemcitabine plus carboplatin, paclitaxel plus carboplatin, vinorelbine plus cisplatin and gemcitabine plus cisplatin were: £999, £1,489, £403 and £795

respectively. Details of the calculations used to determine these costs are presented in tables 24 and 25.

The cost of chemotherapy administration per cycle (table 45) was taken from national reference costs 2007/08[80].

**Table 45: Cost of chemotherapy delivery**[80]

| Comparator | Resource | Cost per cycle |
|---|---|---|
| Gem/carb | 1 x SB12Z (outpatient) + 1 x SB15Z (outpatient) | £307 |
| Pac/carb | 1 x SB12Z (outpatient) | £153 |
| Vin/cis | 1 x SB14Z (Day case and regular day/night) + SB15Z (Day case and regular day/night) | £527 |
| Gem/cis | 1 x SB14Z (Day case and regular day/night) + SB15Z (Day case and regular day/night) | £527 |

After patients receive 5 cycles of chemotherapy they are assumed to return to the hospital on a monthly basis for a consultant assessment, at a cost of £86 per visit, until disease progression. NHS funded transportation to the hospital is assumed to be required for 50% of patients receiving chemotherapy, at an average cost of £28 per journey[80]. An average patient cost of £218 is assumed for the management of chemotherapy induced AEs. In addition, it is assumed that 22% of patients receiving doublet chemotherapy will be given g-CSF for prophylaxis of neutropenia at a cost of £1,284 per treated patient.

**8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?**

In addition to the gefitinib single fixed payment, the other significant cost associated with treatment is the cost of EGFR testing. Currently, this test is not routinely conducted in the NHS in England & Wales. A diagnostic company that already performs this service has agreed to charge [redacted] per test on the basis that they will conduct 7,500 tests per year (i.e. approximately one in five patients with lung cancer will have an EGFR test see table 44). A conservative assumption has been made that the cost of EGFR testing will remain constant over the next 5 years. However, the cost is likely to fall as testing techniques improve and economies of scale are achieved.

Gefitinib is a well-tolerated oral treatment for patient with aNSCLC. In IPASS, AEs leading to permanent discontinuation occurred in 6.9% of patients treated with gefitinib compared with 13.6% receiving paclitaxel + carboplatin. Rash and diarrhoea are the most troublesome adverse events with gefitinib but these are generally self-limiting and readily managed. The cost of AE management (mean cost of £60 per patient) has been included in the budget impact analysis.

### 8.7 Were there any estimates of resource savings? If so, what were they?

In terms of resource savings, gefitinib will assist the NHS in England and Wales in relieving the pressure on the current chemotherapy service, allowing the redeployment of existing consultant, pharmacy and nursing staff resources for the benefit of other patients with cancer. For example, treating 290 EGFR M+ patients with aNSCLC with doublet chemotherapy instead of gefitinib would require around 2,900 outpatient appointments for the chemotherapy delivery (assuming an average of 5 cycles per patient). The hospital pharmacy would need to prepare 2,900 intravenous chemotherapy treatments in dedicated isolator cabinets in pharmaceutical clean rooms, both of which require high levels of capital investment.

In addition, gefitinib will require less hospital resource in terms of the management of treatment related AEs. In IPASS, CTC grade 3/4 AEs occurred in 28% of patients treated with gefitinib versus 61% that received doublet chemotherapy.

### 8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None have been identified.

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## *10.5 Appendix 5: AstraZeneca Single Payment Access Scheme*

By paying AZ a one off single fixed payment (also referred contractually as the AZ SPA Scheme registration fee) per NHS patient regardless of the duration of the cancer treatment (in this case gefitinib), the NHS will in effect be paying AZ for the acquisition cost of the medicine for that NHS patient and the associated peripheral services such as hospital delivery.
The NHS will have the option to sign up to the AZ SPA Scheme which will make gefitinib available to their Non Small Cell Lung Cancer (NSCLC) patients registered under the AZ SPA Scheme at a single fixed payment (also referred contractually as the AZ SPA Scheme registration fee) per NHS patient that covers the duration of their treatment, regardless of how long that may be.

Relevant NHS employees will be able to register their NHS NSCLC patients on to the AZ SPA Scheme using an AZ SPA Scheme Registration Form that will be accessible online via the http://www.simplyaz.co.uk/simply-supply website. By formally registering patients onto the AZ SPA Scheme, the NHS Trust will be signing up to and be bound by our AZ SPA Scheme Terms and Conditions (details of which shall also be available to the NHS on line).

Through the website relevant NHS users will:

- Access the AZ SPA Scheme terms and conditions as well as the terms and conditions of sale of gefitinib outside the AZ SPA Scheme
- Details of the actual AZ SPA Scheme fixed payment (also referred contractually as the AZ SPA Scheme registration fee) payable to AZ by the NHS per patient will be kept confidential between the individual NHS Trusts and AZ. This information will only be accessible online to relevant NHS healthcare professionals within those NHS Trusts via an additional secure log in (with automated identification and verification of legitimate NHS email addresses)
- Have access to a NSCLC patient registration form that will allow the appropriate NHS users to register individual NSCLC patient who will receive gefitinib. The AZ SPA Scheme Registration Form that will be accessible online via the http://www.simplyaz.co.uk/simply-supply website
- Have access to all appropriate contact details to ask any questions about the AZ SPA Scheme and supply of gefitinib.
To make the AZ SPA Scheme workable and to avoid inequalities across the NHS, AstraZeneca will submit one single payment at the national level for England, Wales and Scotland.

In 2009, AZ will submit the level of the one off single fixed payment to NICE, which will conduct a single technology appraisal (STA) to establish its cost-effectiveness. AZ will submit the level of the one off single fixed payment to SMC in early 2010.
To enable a future value-based payment adjustment, AZ will analyse anonymous data on duration of therapy from those patients receiving in this case, gefitinib, and this will be used to indicate the clinical value of the treatment. A subsequent NICE appraisal of duration of therapy data will assess the single fixed payment to ensure that it represents value for money.

Outside of the AZ SPA Scheme, gefitinib will only be available to be purchased at the NHS List Price and for such purchases there will be no need to register specific patients using the AZ SPA Scheme Registration Form. Purchases at list price per pack will be subject to AZ's standard terms and conditions of sale of AZ products