Gefitinib (Iressa) with chemotherapy for EGFR-positive non-small cell lung cancer – second line

SUMMARY

Gefitinib (Iressa) is intended to be used as second line therapy in combination with chemotherapy for the treatment of non-small cell lung cancer (NSCLC) in patients who have progressed despite prior gefitinib treatment. If licensed, it will provide an additional treatment option for this patient group. Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. It is currently licensed in the EU for the treatment of locally advanced or metastatic EGFR mutation positive NSCLC in adults.

In the UK, lung cancer is the most common cause of cancer-related death in men and women. NSCLC accounts for around 90% of all lung cancers. There were 35,406 new diagnoses of lung cancer in England and Wales in 2009, and in 2010, 29,914 deaths were registered. One-year survival rates are estimated to be 29% for men and 33% for women, with five-year survival rates falling to 8% and 9% respectively. The majority of newly diagnosed patients will have advanced disease that is incurable at diagnosis, with a five-year survival rate of less than 1%.

Treatment is dependent on the stage of disease and current second line options include: docetaxel or erlotinib monotherapy, pemetrexed and crizotinib. Gefitinib in combination with chemotherapy is currently in a phase III clinical trial comparing its effect on progression-free survival against treatment with placebo in combination with chemotherapy. This trial is expected to complete in 2015.
TARGET GROUP

- Non-small cell lung cancer (NSCLC): EGFR mutation-positive – second line in patients who have progressed following first line gefitinib therapy; in combination with chemotherapy.

TECHNOLOGY

DESCRIPTION

Gefitinib (Iressa; ZD1839) is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. The epidermal growth factor and its receptor have been identified as key drivers in the process of cell growth and proliferation for both normal and cancer cells. EGFR activating mutation within a cancer cell is an important factor in the promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors, and facilitating the processes of metastasis. Gefitinib is administered orally at 250mg once daily, in combination with doublet chemotherapy.

Gefitinib is currently licensed in the EU for the treatment of locally advanced or metastatic, EGFR mutation positive NSCLC in adults. Recognised adverse effects (>10%) include metabolism and nutrition disorders, gastrointestinal disorders, hepatobiliary disorders, skin and subcutaneous tissue disorders and asthenia.

Gefitinib is in phase II trials for bladder cancer, brain metastases and glioblastoma.

INNOVATION and/or ADVANTAGES

If licensed, continuing gefitinib therapy in combination with chemotherapy will offer an additional treatment option for this patient group.

DEVELOPER

AstraZeneca UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In a phase III clinical trial.

PATIENT GROUP

BACKGROUND

NSCLC accounts for around 90% of all lung cancers and consists of three common subtypes, namely squamous cell carcinoma, adenocarcinoma and large cell carcinoma. NSCLC with EGFR activating mutations is considered to be a genetically distinct form of lung cancer which is most common in people with adenocarcinoma, non-smokers, people of Indian, Bangladeshi or Pakistani origin, and females. Overexpression of EGFR has been detected in 10-15% of NSCLC.

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*a* Gemcitabine with cisplatin or carboplatin, or pemetrexed with cisplatin or carboplatin.
NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).

CLINICAL NEED and BURDEN OF DISEASE

In the UK, lung cancer is the most common cause of cancer-related death in men and women. In 2009, there were 35,406 new cases of lung cancer in England and Wales (representing approximately 48 cases per 100,000 population), and in 2010, 29,914 deaths were registered in England and Wales (approximately 39 deaths per 100,000 population). In England and Wales, one-year survival rates are estimated to be 29% for men and 33% for women, with five-year survival rates falling to 8% and 9% respectively. Around 5.5% of lung cancers are considered cured with currently available treatments. About 90% of lung cancer mortality among men and 80% among women is attributable to smoking.

Approximately 78% of newly diagnosed patients will have advanced (stage III or IV) disease that is incurable at diagnosis, with a five-year survival rate of less than 1%. EGFR mutation-positive disease occurs in 10-15% of NSCLCs. In 2011-12, there were 85,009 hospital admissions for cancer of the bronchus and lung (ICD-10 C34) in England, accounting for 104,814 finished consultant episodes and 302,720 bed days.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of TA162 and TA175) (ID620). Expected June 2014.
EXISTING COMPARATORS and TREATMENTS

Treatment for NSCLC aims to relieve symptoms, control disease progression, improve quality of life and increase survival. Treatment is dependent on the stage of the disease and options include surgery, chemotherapy (for patients with a good performance status\(^b\)) and radiation therapy, alone or in combination\(^7\). Second line treatment options include\(^{21,31,32}\):

- Docetaxel (monotherapy) – a mitosis inhibitor.
- Erlotinib (monotherapy) – an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).
- Pemetrexed – a thymidylate synthase and dihydrofolate reductase inhibitor.
- Gefitinib – an EGFR TKI (NICE unable to recommend due to lack of evidence from manufacturer).
- Crizotinib – a TKI licensed for previously treated ALK-positive advanced NSCLC (NICE technology appraisal currently in development).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>IMPRESS, NCT01544179; gefitinib vs placebo, both in combination with cisplatin and pemetrexed; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AstraZeneca.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^{33}).</td>
</tr>
</tbody>
</table>

\(^b\) 0 or 1 on the World Health Organisation performance status scale, or a Karnofsky score of 80-100.
<table>
<thead>
<tr>
<th>Location</th>
<th>EU and other countries.</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=250 (planned); aged 18 years and older; NSCLC; EGFR mutation positive; disease progression following first line gefitinib.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to gefitinib, oral, 250mg or placebo; both in combination with pemetrexed, IV, 500mg/m² and cisplatin, IV, 75mg/m², every 21 days for a maximum of 6 cycles.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression; follow-up until 12 months after primary endpoint analysis.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Progression free survival.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Overall survival; objective response rate; disease control rate; health related quality of life; safety and tolerability.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>2015.</td>
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### ESTIMATED COST and IMPACT

#### COST

The cost of gefitinib is not yet known. The costs of other selected treatments for NSCLC are summarised below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose(^c)</th>
<th>Cost(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>75mg/m², IV, every 21 days</td>
<td>£720.10 per dose</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>150mg, oral, once daily</td>
<td>£1,631.53 per 30 days</td>
</tr>
<tr>
<td>Pemetrexed (Alimta)</td>
<td>500mg/m², IV, every 21 days</td>
<td>£1,600 per dose</td>
</tr>
</tbody>
</table>

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

**Impact on Services**

- Increased use of existing services
- Decreased use of existing services
- Need for new services
- None identified

**Impact on Costs**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other reduction in costs:
- None identified

\(^c\) Based on an average surface area of 1.88m². Assumes wastage.
Other Issues

☐ Clinical uncertainty or other research question  ☒ None identified

REFERENCES


