BIBF 1120 for advanced and/or metastatic non-small cell lung cancer – second line

December 2009

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
BIBF 1120 for advanced and/or metastatic non-small cell lung cancer – second line

**Target group**
- Non-small cell lung cancer (NSCLC): advanced and/or metastatic stage IIIB/IV or recurrent – second line; in combination with pemetrexed (Alimta) or docetaxel (Taxotere) after failure of prior chemotherapy.

**Technology description**
BIBF 1120 is an oral antiangiogenic inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR). Inhibition of these growth factors limits the supply of oxygen and nutrients to cancer cells by reducing vascularisation of tumours, thereby suppressing tumour growth. BIBF 1120 is orally administered in combination with pemetrexed (Alimta) or docetaxel (Taxotere) and is being trialled at doses of 150-250mg twice daily.

BIBF 1120 is also in phase III clinical trials for advanced ovarian cancer and phase II clinical trials for colorectal cancer, renal cell carcinoma, and hepatocellular carcinoma.

**Innovation and/or advantages**
BIBF 1120 is the first antiangiogenic agent to act on three different types of receptors involved in tumour angiogenesis. BIBF 1120 may, in combination with standard chemotherapy, prolong the disease control of patients with NSCLC who have failed one prior line of chemotherapy. In addition, the combination of BIBF 1120 with docetaxel would provide a treatment option for patients with squamous cell lung cancer, for which pemetrexed is not licensed.

**Developer**
Boehringer Ingelheim.

**Availability, launch or marketing dates, and licensing plans**
In phase III clinical trials.

**NHS or Government priority area**
This topic is relevant to the NHS Cancer Plan (2000) and Cancer Reform Strategy (2007).

**Relevant guidance**

**NICE technology appraisals in development**
- Vandetanib within its licensed indications, for the second and subsequent line treatment of non-small cell lung cancer after previous platinum containing chemotherapy. Suspended November 2010.
- Erlotinib, in combination with bevacizumab for the maintenance treatment of non-squamous advanced or metastatic non-small cell lung cancer after previous platinum containing chemotherapy. Expected June 2011.
NICE published technology appraisals
- Topotecan for the treatment of relapsed small cell lung cancer. 20096.
- Pemetrexed for the first line treatment of non-small cell lung cancer. 20097.
- Pemetrexed for the treatment of non-small cell lung cancer. 20079.

NICE interventional procedure guidance
- Percutaneous radiofrequency ablation for primary and secondary lung cancers. 200610.
- Photodynamic therapy for localised inoperable endobronchial cancer. 200511.
- Cryosurgery for malignant endobronchial obstruction. 200512.
- Photodynamic therapy for advanced bronchial carcinoma. 200413.

NICE clinical guidelines

Other Guidance
- SIGN. Management of patients with lung cancer. 200516.
- Cancer Services Collaborative Improvement Partnership. Lung cancer service improvement guide. 200417.

Clinical need and burden of disease
Lung cancer is the most common cause of cancer-related death in men, and the second most common cause of cancer-related death after breast cancer in women. In 2007, there were 35,016 new cases of lung cancer in England and Wales18,19 (an incidence of around 64 cases per 100,000 population) and 29,574 registered deaths (an incidence of around 54 deaths per 100,000 population)20. In England and Wales lung cancer has a one-year survival rate of 25% and a five-year survival rate of 7%21.

NSCLC accounts for approximately 80% of all lung cancers, with the main types being squamous cell carcinoma, adenocarcinoma and large cell carcinoma14. Approximately 75% of newly diagnosed NSCLC patients have advanced (stage III or IV) disease in England and Wales (approximately 21,010 patients)22 which has five-year survival rates of less than 1%23.

In late stage NSCLC, treatment offers the patient the possibility of symptom relief, improved disease control, better quality of life and increased survival. However, not all patients with advanced disease are fit enough to receive systemic treatment24. Approximately 25% of patients with advanced NSCLC receive first-line chemotherapy and around 20-40% of these (1,050-2,100 patients) may be eligible to receive second-line therapy21.

Existing comparators and treatments
Second line therapy options for NSCLC include:
- Docetaxel (Taxotere) - a mitosis inhibitor.
- Erlotinib (Tarceva) - an epidermal growth factor receptor antagonist (not licensed after failure of second-line docetaxel therapy8).
- Pemetrexed (Alimta) - a thymidylate synthase and dihydrofolate reductase inhibitor - licensed but not currently recommended by NICE\textsuperscript{7} (not licensed for predominantly squamous cell histology).

There is currently no approved therapy for NSCLC patients who have progressed after previous cytotoxic chemotherapy or who have developed resistance after initial clinical benefit.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>LUME-Lung 1 (1199.13); BIBF1120 and docetaxel vs placebo and docetaxel; phase III.</th>
<th>LUME-Lung 2 (1199.14); BIBF1120 and pemetrexed vs placebo and pemetrexed; phase III</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Boehringer Ingelheim.</td>
<td>Boehringer Ingelheim.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{25}.</td>
<td>Trial registry\textsuperscript{26}.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (including UK), USA, Canada, and other countries.</td>
<td>EU (excluding UK), USA, and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, controlled.</td>
<td>Randomised, controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=1,300 (planned); adults; advanced (stage IIIB or IV) or recurrent. NSCLC; progressed after first line chemotherapy. Randomised to BIBF 1120 200mg twice daily and docetaxel\textsuperscript{a}, or placebo and docetaxel until disease progression or withdrawal criteria are met.</td>
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<td>Follow-up</td>
<td>Until disease progression, loss to follow-up or death.</td>
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<tr>
<td>Primary outcome</td>
<td>Progression free survival (PFS)</td>
<td>PFS.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Overall survival, adverse events (AEs), tumour response, health related quality of life (HRQL).</td>
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</tr>
</tbody>
</table>

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<tr>
<th>Trial</th>
<th>Relapsed advanced NSCLC; phase II.</th>
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<tr>
<td>Sponsor</td>
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<tr>
<td>Status</td>
<td>Trial complete and published in abstract.</td>
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<tr>
<td>Source of information</td>
<td>Abstract\textsuperscript{29}.</td>
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<tr>
<td>Location</td>
<td>Germany.</td>
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<tr>
<td>Design</td>
<td>Randomised, uncontrolled.</td>
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<td>Participants and</td>
<td>n=73; adults; ECOG\textsuperscript{c} score 0-2, relapsed stage IIIB/IV NSCLC, after first or second line chemotherapy.</td>
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</table>

\textsuperscript{a} Docetaxel 75mg/m\textsuperscript{2} as a one hour intravenous (IV) infusion every three weeks\textsuperscript{27}.

\textsuperscript{b} Pemetrexed 500mg/m\textsuperscript{2} as an IV infusion over 10 minutes every three weeks\textsuperscript{28}.

\textsuperscript{c} The ECOG PS (Eastern Cooperative Oncology Group Performance Status) scale assesses a patient’s disease progression, living abilities, and determines appropriate treatment and prognosis. The scale runs from 0-5 with: 0=asymptomatic; 1=symptomatic but completely ambulatory; 2=symptomatic, <50% in bed during the day; 3=Symptomatic, >50% in bed, but not bedbound; 4=bedbound; 5=death.
Initially randomised to BIBF 1120 250mg or 150mg twice daily. In the event of dose limiting toxicity, single dose reduction to open label treatment with 150mg or 100mg twice daily.

Follow-up

Until disease progression.

Primary outcome/s

PFS, OTR.

Key results

Median PFS 1.6 months (all patients); no significant difference between treatment arms; stable disease 48% without objective tumour response. ECOG score 0 or 1 (n= 57): median PFS 2.9 months; 3 and 5 month PFS rate 46% and 31%; no significant difference between treatment arms; stable disease 59%.

Adverse effects (AEs)

Dose limiting grade 3 and 4 toxicities: 27% and 2.8% for 250mg and 150 mg twice daily respectively (p=0.006). Grade 1 or 2 AEs: nausea (41%), diarrhoea (41%), vomiting (33%), fatigue (29%), abdominal pain (22%). Grade 3 and 4 toxicities: nausea (8%), diarrhoea (7%), vomiting (4%), abdominal pain (4%), AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) elevations (5.4%).

Estimated cost and cost impact

The cost of BIBF 1120 is not yet known.

Claimed or potential impact – speculative

Patients

- Reduced mortality or increased length of survival
- Other:
  - Reduction in associated morbidity or Improved quality of life for patients and/or carers
  - None identified
  - Quicker, earlier or more accurate diagnosis or identification of disease

Services

- Increased use
- Decreased use
  - None identified
  - Other: may delay need for palliative care
  - Staff requirements

Costs

- Increased unit cost compared to alternative
  - New costs: additional costs (if in combination)
  - Other:
  - Increased costs: more patients coming for treatment
  - Increased costs: capital investment needed
  - Savings:
  - None identified

References

28 Alimta 100mg/500mg powder for concentrate for solution for infusion, Summary of Product Characteristics: http://emc.medicines.org.uk/medicine/15513/SPC/Alimta+100mg+500mg+powder+for+concentrate+for+solution+for+infusion/ Accessed 8 December 2009.
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