

# National Horizon Scanning Centre

## Vandetanib (Zactima) for advanced or metastatic non-small cell lung cancer

**December 2007**



This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

## **Vandetanib (Zactima) for advanced or metastatic non-small cell lung cancer**

### **Target group**

- Non-small cell lung cancer (NSCLC) – locally advanced or metastatic (stage IIIB and IV) disease; second-line therapy.

### **Technology description**

Vandetanib (Zactima, ZD6474, AZD6474) is a once-daily, oral antiangiogenic vascular endothelial growth factor (VEGF) receptor-2, epidermal growth factor receptor (EGFR) and rearranged during transfection (RET) tyrosine kinase inhibitor. Vandetanib works by inhibiting both the development of the tumour's blood supply and the growth and survival of the tumour itself. It is intended to be administered as up to 300mg once daily either in combination with docetaxel or pemetrexed, or as a monotherapy.

Vandetanib is also in phase II development for medullary thyroid cancer, myeloma, breast, brain and prostate cancer.

### **Innovation and/or advantages**

Vandetanib is the first in a new drug class of combined tyrosine kinase inhibitors and may provide longer-lasting anti-tumour effects. Vandetanib may also offer advantages compared with other agents, including oral bioavailability, more flexible dosing, and different toxicity profiles<sup>1</sup>.

### **Developer**

AstraZeneca.

### **Place of use**

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> Home care – potential for home care delivery                                | <input type="checkbox"/> Community or residential care e.g. district nurses, physio           | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses    |
| <input checked="" type="checkbox"/> Secondary care - non-specialist hospital capable of chemotherapy | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter  | <input type="checkbox"/> Other:   |  |

### **Availability, launch or marketing dates, and licensing plans:**

In Phase II clinical trials.

### **NHS or Government priority area:**

This topic is relevant to the NHS Cancer Plan.

### **Relevant guidance**

#### NICE clinical guideline

- Lung Cancer: the diagnosis and treatment of lung cancer. 2005 (expected review date February 2009)<sup>2</sup>.

#### NICE technology appraisals

- Pemetrexed for the treatment of non-small cell lung cancer. 2007<sup>3</sup>.
- Docetaxel, paclitaxel, gemcitabine and vinorelbine for the treatment of non-small cell lung cancer. 2001 (now replaced by NICE Clinical Guideline on Lung Cancer, 2005)<sup>4</sup>.
- Bevacizumab for non-small cell lung cancer. Expected January 2008<sup>5</sup>.
- Erlotinib for advanced non-small cell lung cancer. Expected April 2008<sup>6</sup>.

- Scottish Intercollegiate Guidelines Network (SIGN): Management of patients with lung cancer. 2005<sup>7</sup>.
- European Society for Medical Oncology (ESMO): Minimum clinical recommendations for the diagnosis, treatment and follow-up of non-small cell lung cancer. 2005<sup>8</sup>.
- US National Comprehensive Cancer Network (NCCN): clinical practice guideline on non-small cell lung cancer. 2007<sup>9</sup>.

### Clinical need and burden of disease

Lung cancer is the most common cause of death in the UK. In England and Wales there were 32,715 new cases diagnosed in 2004, with 28,632 deaths registered in 2005 (around 54 deaths per 100,000 of population)<sup>10</sup>. In England and Wales lung cancer has a one-year survival rate of 25% and a five-year survival rate of 7%<sup>11</sup>.

NSCLC accounts for approximately 80% of all lung cancers. Approximately 75% of newly diagnosed patients already have advanced (stage III or IV) disease<sup>12</sup> (equating to around 24,536 patients in England and Wales), with a five-year survival rate of less than 1%<sup>13</sup>. NICE estimates that around 25% of patients with advanced NSCLC receive first-line chemotherapy<sup>14</sup>. Around 30-40% of these patients may subsequently become candidates for second-line therapy (approximately 1,840-2,450 patients)<sup>15</sup>.

### Existing comparators and treatments

Treatment options for stage IIIB or IV NSCLC include radiation therapy, chemotherapy with radiation therapy, and chemotherapy alone. Chemotherapy may be recommended for patients with non-resectable stage III or IV disease provided they have a good performance status. Current NICE guidance recommends that first-line chemotherapy should include a combination of a platinum drug (cisplatin or carboplatin) and a single third generation drug, such as docetaxel, gemcitabine, paclitaxel or vinorelbine.

Second-line therapy options include:

- docetaxel (Taxotere) monotherapy
- erlotinib (Tarceva) monotherapy – licensed and NICE guidance expected April 2008
- pemetrexed (Alimta) – licensed but not currently recommended by NICE
- bevacizumab (Avastin) – licensed and NICE guidance expected January 2008
- gefitinib (Iressa) – in clinical trials (unlicensed).

### Efficacy and safety

Trial name or code	6474IL/0006; vandetanib plus docetaxel vs docetaxel – refractory. Phase II	6474IL/0003; vandetanib vs gefitinib – second/third-line. Phase II
Sponsor	AstraZeneca	AstraZeneca
Status	Published <sup>16</sup>	Published <sup>17</sup>
Location	USA, Czech Republic, Hungary	Multicentre
Design	Randomised, double blind, placebo-controlled.	Randomised, crossover, double blind.
Participants	N=127; stage IIIB/IV NSCLC after failure of platinum-based therapy. Following open-label run-in, randomised (until disease progression, unacceptable toxicity, or withdrawal of consent) to: <u>Arm A</u> : vandetanib 100mg daily plus	N=168; stage IIIB/IV NSCLC after failure of first-line ± second-line platinum-based therapy. <u>Part 1</u> : Randomised to vandetanib 300mg daily or gefitinib 250mg daily, until disease progression or evidence of

	docetaxel (iv) every 21 days (V-100+D); <u>Arm B</u> : vandetanib 300mg daily plus docetaxel (V-300+D); <u>Arm C</u> : placebo plus docetaxel (D).	toxicity. <u>Part 2</u> : After a 4-week washout period, patients had the option to switch treatment.
Primary outcome	Progression-free survival (PFS).	Progression-free survival (PFS), and safety/tolerability.
Secondary outcomes	Objective response rate, overall survival, safety and tolerability.	Overall survival.
Key results	Median PFS - V-100+D: 18.7 weeks; V-300+D: 17.0 weeks; D alone: 12.0 weeks. Per protocol analysis: V-100+D significantly prolonged PFS versus D alone (HR = 0.64; 95% CI = 0.38-1.05; 1-sided p = 0.037). There was no statistically significant difference in overall survival.	Part 1: median PFS vandetanib: 11.0 weeks; gefitinib: 8.1 weeks (HR = 0.69, 95% CI 0.5-0.96; p = 0.025). Disease control >8 weeks 45% for vandetanib vs 34% for gefitinib. Part 2: disease control in 43% who switched from gefitinib to vandetanib, and in 24% who switched from vandetanib to gefitinib. Overall survival: vandetanib median 6.1 months vs gefitinib: median 7.4 months.
Major adverse effects	Common adverse events included: diarrhoea, rash, and asymptomatic prolongation of corrected QT interval.	Diarrhoea (grade 3/4, 8.4%); rash (grade 3/4, 4.8%); asymptomatic corrected QT prolongation 20.5%.

Trial name + code	D4200C00032/ NCT00312377; vandetanib versus docetaxel – second-line. Phase III	D4200C00044/ NCT00404924; vandetanib monotherapy – refractory. Phase III	D4200C00057/NCT 00364351; vandetanib versus erlotinib – refractory. Phase III	D4200C00036/NCT 00418886; vandetanib with pemetrexed – second-line. Phase III
Sponsor	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca
Status	In progress	In progress	In progress	In progress
Location	Multicentre	Multicentre	Multicentre	Multicentre
Design	Randomised, double blind, active control.	Randomised, double blind placebo-control.	Randomised, double blind, active control.	Randomised, double blind placebo-control.
Participants	N=1,240; stage IIIB/IV NSCLC after failure of first-line treatment. Vandetanib 100mg with docetaxel or docetaxel alone.	N=930; stage IIIB/IV NSCLC previously treated with anti-EGFR therapy. Vandetanib 300mg or placebo.	N=1,150; stage IIIB/IV NSCLC after failure of 1-2 prior regimens. Vandetanib 300mg or erlotinib 150mg.	N=508; stage IIIB/IV NSCLC after failure of first-line treatment. Vandetanib 100mg with pemetrexed or pemetrexed alone.
Primary outcome	Progression-free survival.	Progression-free survival.	Progression-free survival.	Progression-free survival.
Secondary outcomes	Overall survival.	Overall survival.	Overall survival.	Overall survival.

### Estimated cost and cost impact

The cost of vandetanib is not yet known.

Drug	Dose	12-week cost <sup>a</sup>
Docetaxel	75mg/m <sup>2</sup> iv every 21 days	£4,278
Erlotinib	1 x 150mg oral tablet daily	£4,568 (pro-rata)
Bevacizumab	7.5 - 15mg/kg iv every 21 days	£4,668 - £9,336
Pemetrexed	500mg/m <sup>2</sup> iv every 21 days	£6,400

### Potential or intended impact – speculative

#### Patients

- |   |  |   |
|---|--|---|
| <input checked="" type="checkbox"/> Reduced morbidity   | <input type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other:                                  | <input type="checkbox"/> None identified  |

#### Services

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> Increased use                                 | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use – lower incidence of toxicities | <input type="checkbox"/> Other:                          | <input checked="" type="checkbox"/> None identified |

#### Costs

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative      | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input checked="" type="checkbox"/> New costs: additive treatment option. | <input type="checkbox"/> Savings:  | <input type="checkbox"/> Other:                                     |

### References

- <sup>1</sup> Hanrahan EO & Heymach JV. Vascular endothelial growth factor receptor tyrosine kinase inhibitors vandetanib (ZD6474) and AZD2171 in lung cancer. *Clin Cancer Res* 2007; 13 (15): 4617-4622.
- <sup>2</sup> National Institute for Health and Clinical Excellence. Lung Cancer: The diagnosis and treatment of lung cancer. Clinical Guideline 24, February 2005.
- <sup>3</sup> National Institute for Health and Clinical Excellence. Pemetrexed for the treatment of non-small cell lung cancer. Technology Appraisal 124, August 2007.
- <sup>4</sup> National Institute for Health and Clinical Excellence. Docetaxel, paclitaxel, gemcitabine and vinorelbine for the treatment of non-small cell lung cancer. Technology Appraisal 26, 2001 (now replaced by Clinical Guideline 24).
- <sup>5</sup> National Institute for Health and Clinical Excellence. Bevacizumab for the treatment of non-small cell lung cancer. Technology Appraisal in development - publication expected January 2008.
- <sup>6</sup> National Institute for Health and Clinical Excellence. Erlotinib for the treatment of advanced non-small cell lung cancer. Technology Appraisal in development - publication expected April 2008.
- <sup>7</sup> Scottish Intercollegiate Guidelines Network (SIGN): Management of patients with lung cancer. Guideline 80, February 2005.
- <sup>8</sup> ESMO: Minimum clinical recommendations for the diagnosis, treatment and follow-up of non-small cell lung cancer (NSCLC). *Annals of Oncol* 2005; 16 (1): 128-129.
- <sup>9</sup> National Comprehensive Cancer Network (NCCN): clinical practice guideline on non-small cell lung cancer, September 2007.
- <sup>10</sup> Cancer Research UK, Cancer Stats Lung cancer and smoking – UK, July 2007
- <sup>11</sup> Coleman M, Rachet B, Woods L et al. Trends in socio-economic inequalities in cancer survival in England and Wales up to 2001, *British Journal of Cancer* 2004; 90(7): 1367-73.
- <sup>12</sup> Liverpool Reviews and Implementation Group, ERG Report – Pemetrexed for the treatment of relapsed non-small cell lung cancer, September 2006, London: National Institute for Health and Clinical Excellence.

<sup>a</sup> British National Formulary edition 53, March 2007. Estimated costs based on an average body weight of 62 kg and body surface area of 1.7 m<sup>2</sup>.

- <sup>13</sup> National Collaborating Centre for Acute Care, The diagnosis and treatment of lung cancer: methods, evidence and guidance; February 2005, London: National Collaborating Centre for Acute Care.
- <sup>14</sup> National Institute for Clinical Excellence (NICE) technology appraisal in development: Bevacizumab for the treatment of non small cell lung cancer – final scoping document April 2007, accessed online 20 Nov 2007 at <http://www.nice.org.uk>
- <sup>15</sup> Hu C, Davies AM, Lara PN et al. Second-line treatment for advanced-stage non-small cell lung cancer: current and future options. *Clin Lung Cancer* 2006; 7(4): S118-25.
- <sup>16</sup> Heymach JV, Johnson BE, Prager D et al. Randomised, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non-small-cell lung cancer. *J Clin Oncol* 2007; 25(27): 4270-4277.
- <sup>17</sup> Natalie RB, Bodkin D, Govindan R et al. ZD6474 versus gefitinib in patients with advanced NSCLC: final results from a two-part, double-blind, randomised Phase II trial. *Proc Am Soc Clin Oncol (Abstract)* 2006; 24(18S): 7000.

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