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Pemetrexed (Alimta) for locally advanced and/or metastatic non-small cell lung cancer (NSCLC) – first line, induction and maintenance.

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Pemetrexed (Alimta) for locally advanced and/or metastatic non-small cell lung cancer (NSCLC) – first line, induction and maintenance.

Target group

- Non-small cell lung cancer (NSCLC): stage IIIB or IV; non-squamous histology – first line; induction and maintenance (where disease has not progressed).

Technology description

Pemetrexed disodium (Alimta, LY231514) is a multi-targeted inhibitor of three key enzymes in the folate metabolic pathway: thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. It leads to depletion of fully reduced folate, ultimately resulting in disruption to crucial metabolic processes essential for cell replication. Pemetrexed is administered by intravenous (IV) infusion at 500mg/m^2 every 3 weeks in combination with IV cisplatin at 75mg/m^2, vitamin supplementation, and dexamethasone during the induction phase (cycles 1-4); followed by a maintenance phase of IV pemetrexed 500mg/m^2 every 3 weeks along with best supportive care, vitamin supplementation and dexamethasone until disease progression.

Pemetrexed is currently licensed in the EU for the following indications:

- In combination with cisplatin for the treatment of chemotherapy-naïve patients with unresectable malignant pleural mesothelioma.
- As monotherapy for second line treatment of locally advanced and/or metastatic non-squamous NSCLC.
- In combination with cisplatin for first line treatment of locally advanced or metastatic non-squamous NSCLC in chemotherapy-naïve patients.
- As monotherapy for maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately following platinum-based chemotherapy.

Recognised adverse effects include: allergic or hypersensitivity reactions, dehydration, erythema multiforme, eye or eyesight problems, fever, heartburn, increased tear production, indigestion, infections, itching, kidney problems, neuropathies, oedema, stomach pain and taste changes[1].

Pemetrexed is in phase III clinical trials for head and neck cancer, pancreatic cancer, mesothelioma and NSCLC (in combination with carboplatin and bevacizumab); and in phase II trials for breast cancer, NSCLC (first line, in combination with carboplatin), osteosarcoma, renal cancer, bladder cancer, gastrointestinal cancer, leukaemia, colorectal cancer, endometrial cancer, soft-tissue sarcoma, non-Hodgkin's lymphoma and ovarian cancer.

Innovation and/or advantages

If licensed for this indication, patients who have demonstrated a response from pemetrexed/cisplatin induction therapy will be able to continue on pemetrexed maintenance therapy.

Developer

Eli Lilly and Company.

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 appraisal in development. Erlotinib monotherapy for the maintenance of non-small cell lung cancer. Expected October 2010[2].
- NICE technology appraisal in development. 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. Suspended July 2010[3].
- NICE technology appraisal in development. Cetuximab for the treatment of non-small cell lung cancer. Suspended May 2009[4].
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. 2010[5].
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Clinical need and burden of disease

In 2008, 30,326 deaths occurred from lung cancer in England and Wales (ICD10 C33-34)[19]. It is the second most common cancer diagnosed in the UK after breast cancer and the most common cause of cancer death in the UK, accounting for more than 1 in 5 deaths[20]. In 2007, there were 33,825 new diagnoses in England and Wales (UK incidence of around 64 per 100,000 population), with more cases diagnosed in men, though rates in

women are rising.[21]. Lung cancer is rarely diagnosed in people younger than 40, and its incidence peaks between ages 75-84[19]. Survival rates are higher the earlier the cancer is diagnosed, however lung cancer is often diagnosed late and long term survival is poor, with less than 10% of patients surviving for 5 years or more after diagnosis[18].

NSCLC accounts for around 80% of lung cancers; the three main types being squamous cell carcinoma, adenocarcinoma and large cell carcinoma[10]. The non-squamous types - adenocarcinoma and large cell carcinoma - account for around 27% and 10% respectively, of all UK lung cancer cases[10]. In England and Wales, approximately 75% of newly diagnosed NSCLC patients have advanced (stage III or IV) disease (approximately 21,000 patients)[22], which has a five-year survival rate of less than 1%[10].

Existing comparators and treatments

In late stage NSCLC, treatment aims to relieve symptoms, improve disease control, improve quality of life, and increase survival. Treatment options for stage IIIB or IV NSCLC include radiation therapy, chemotherapy with radiation therapy and chemotherapy alone. Chemotherapy may be recommended for patients provided they have a good performance status[a,10].

First line chemotherapy regimens for advanced NSCLC include[10,23]:

- A combination of single third-generation drugs (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin), or pemetrexed with cisplatin in non-squamous pathology.
- Single agent chemotherapy with a third generation drug for patients who cannot tolerate a platinum combination.
- Gefitinib in the presence of tumours with EGFR sensitising mutations.
- Bevacizumab plus platinum containing chemotherapy (not recommended by NICE).

Maintenance therapy with pemetrexed in non-squamous pathology for tumours that have not progressed following first line platinum-based chemotherapy (not containing pemetrexed).

Efficacy and safety

Trial	NCT00087711; adults; pemetrexed and cisplatin vs gemcitabine and cisplatin; phase III.	NCT00102804; adults; pemetrexed maintenance and best supportive care vs placebo maintenance and best supportive care; phase III.	NCT00789373; adults; pemetrexed and cisplatin induction, pemetrexed maintenance and best supportive care vs pemetrexed and cisplatin induction, placebo maintenance and best supportive care; phase III.
Sponsor	Eli Lilly and Company Limited.	Eli Lilly and Company Limited.	Eli Lilly and Company Limited.
Status	Published.	Published.	Ongoing.
Source of information	Publication[24], trial registry[25].	Publication[26], trial registry[27].	Publication[28], trial registry[29].
Location	EU (inc UK), USA, Canada and other countries.	EU, USA and other countries.	EU (inc UK), Canada, Australia and India.
Design	Randomised, active-	Randomised, placebo-	Randomised, placebo-

[a] 0 or 1 on the World Health Organisation performance status scale, or a Karnofsky score of 80-100.

	controlled.	controlled.	controlled.
Participants and schedule	n=1725; adults; NSCLC; stage IIIB not eligible for curative radiotherapy or surgery, or stage IV; chemotherapy-naïve. Randomised to: pemetrexed 500mg/m^2 and cisplatin 75mg/m^2 IV, every 3 weeks for 6 cycles; or gemcitabine 1250mg/m^2 IV on days 1 and 8, of a 21 day cycle and cisplatin 75mg/m^2 IV every 3 weeks, both for 6 cycles.	n=663; adults; NSCLC stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV; not progressed following 4 cycles of induction therapy (not including pemetrexed). Randomised to: pemetrexed 500mg/m^2 IV, every 3 weeks or placebo IV, every 3 weeks, both until disease progression.	n=900 (planned); adults; stage IIIB or IV non-squamous NSCLC. Randomised to: Arm 1: pemetrexed 500mg/m^2 and cisplatin 75mg/m^2 IV, every 3 weeks for 4 cycles, followed by pemetrexed maintenance therapy 500mg/m^2 IV, every 3 weeks until disease progression, and best supportive care. Arm 2: pemetrexed 500mg/m^2 and cisplatin 75mg/m^2 IV, every 3 weeks for 4 cycles, followed by placebo maintenance therapy IV, every 3 weeks until disease progression, and best supportive care.
Follow-up	Active treatment period 18 weeks; 2 year follow-up.	Active treatment period until disease progression or treatment discontinuation; follow-up every 90 days until death.	Active treatment until disease progression or treatment discontinuation; follow-up every 90 days until death or study closure.
Primary outcome	Overall survival (OS).	PFS.	PFS.
Secondary outcomes	Progression free survival (PFS); time to progressive disease; duration of response; time to treatment failure.	OS; time to progressive disease; time to worsening of symptoms; objective tumour response; adverse events; individual symptom scores and quality of life using the Lung Cancer Symptoms Scale (LCSS).	OS; EQ-5D[b]; resource utilisation; objective tumour response.
Key results	For pemetrexed/cisplatin (PC) and gemcitabine/cisplatin (GC) respectively (months, 95% CIs): median OS, all patients, 10.3 (CI 9.8, 11.2) vs 10.3 (CI 9.6,10.9); non-squamous patients, 11.8 (CI 10.4, 13.2) vs 10.4 (CI 9.6, 11.2); median PFS, all patients, 4.8 (CI 4.6, 5.3) vs 5.1 (CI 4.6, 5.5); non-squamous patients, 5.3 (CI 4.8, 5.7) vs 4.7 (CI 4.4, 5.4).	For pemetrexed and placebo respectively (months, range): median PFS, all patients, 4.0 (3.1-4.4) vs 2.0 (1.5-2.8) (p<0.0001); median OS, all patients, 13.4 (11.9-15.9) vs 10.6 (8.7-12.0) (p=0.012); complete response (CR) + partial response (PR) + stable disease (SD), all patients, 52% vs 33% (p<0.0001); median PFS, non-squamous patients, 4.4 (4.0-5.6) vs 1.8 (1.5-2.8) (p<0.0001); median OS,	-

[b] EuroQol EQ-5D questionnaire: a standardised instrument measuring health outcomes in 5 dimensions.

		non-squamous patients, 15.5 (13.2-18.1) vs 10.3 (8.1-12.0) (p=0.002); CR+PR+SD, non-squamous patients, 58% vs 33% (p<0.0001).	
Expected reporting date	-	-	Estimated study completion date: June 2011.
Adverse effects (AEs)	For PC and GC respectively: neutropenia, 15% vs 27%; anaemia 6% vs 10%; thrombocytopenia 4% vs 13% (all p≤0.001); febrile neutropenia 1% vs 4% (p=0.002); alopecia 12% vs 21% (p<0.001); nausea 7% vs 4% (p=0.004).	AEs >5%: neutropenia (6%), anaemia (15%), leukopenia (6%), raised alanine aminotransferase (ALT) (10%), aspartate aminotransferase (8%), fatigue (24%), anorexia (19%), nausea (19%), vomiting (9%), sensory neuropathy (9%), mucositis/stomatitis (7%).	-

Trial	NCT00051506; adults; pemetrexed with cisplatin vs pemetrexed with carboplatin; phase II.	NCT00402051; adults; pemetrexed with cisplatin vs pemetrexed with carboplatin; phase II.	NCT00606021; adults; pemetrexed maintenance and best supportive care vs best supportive care; phase II.
Sponsor	Eli Lilly and Company Limited.	Eli Lilly and Company Limited.	Eli Lilly and Company Limited.
Status	Complete.	Complete.	Ongoing.
Source of information	Publication[30], trial registry[31].	Trial registry[32], manufacturer.	Trial registry[33].
Location	USA.	Germany.	Egypt, Lebanon and Saudi Arabia.
Design	Randomised, active-controlled.	Randomised, active-controlled.	Randomised, active-controlled.
Participants and schedule	n=78; adults. Randomised to pemetrexed 500mg/m^2 IV, with cisplatin 75mg/m^2 or carboplatin AUC[c] IV, every 3 weeks for 6 cycles.	n=133; adults. Randomised to pemetrexed 500mg/m^2 IV, with cisplatin 75mg/m^2 or carboplatin AUC IV, every 3 weeks for 6 cycles.	n=100 (planned); adults; non-squamous NSCLC; completed pemetrexed with cisplatin induction treatment. Randomised to pemetrexed 500mg/m^2 IV, every 3 weeks for 6 cycles, and best supportive care or best supportive care.
Follow-up	Active treatment period 18 weeks; follow-up until death.	Active treatment period 18 weeks; follow-up until death (up to 12 months).	Active treatment period 18 weeks; follow-up until death or study completion.
Primary outcome	Tumour response.	PFS.	PFS.
Secondary outcomes	CR; PR; progressive disease (PD); time to	OS; tumour response; time to treatment failure.	OS; tumour response.

[c] Area Under Curve - carboplatin dosage is calculated from sex, age, weight, height (in obese patients) serum creatinine and target AUC for carboplatin.

	disease progression (TTP); OS.		
Key results	For pemetrexed with cisplatin and pemetrexed with carboplatin respectively, (95% CIs): PR, 35% (20.6, 51.7) vs 39.5% (24.0, 56.6); stable disease, 35% (20.6, 51.7) vs 26.3% (13.4, 43.1); PD, 10.0% (2.8, 23.7) vs 18.4% (7.7, 34.3); overall response rate, 35.0% (20.6, 51.7) vs 39.5% (24.0, 56.6); median duration of response, months (CR or PR), 4.3 (2.9, 6.1) vs 4.4 (3.2, 9.0); median OS, months, 7.6 (4.9, 10.3) vs 10.4 (7.4, 12.0).	For pemetrexed with cisplatin and pemetrexed with carboplatin respectively, (95% CIs): PFS, 52.8% (40.3, 65.3), 39.3% (27.8, 50.8); OS, months, 11.7 (9.2, 14.9), 8.9 (6.0, 12.2).	
Expected reporting date	-	Study completion date: May 2009.	Estimated study completion date: November 2010.
Adverse effects (AEs)	AEs >5%, pemetrexed with cisplatin and pemetrexed with carboplatin respectively: anaemia 10.5% vs 5.7%; neutropenia 15.8% vs 20.0%; thrombocytopenia 13.2% vs 22.9%; dyspnoea 5.3% vs 20.0%; nausea 15.8% vs 14.3%; vomiting 7.9% vs 14.3%; nervous system toxicity 15.8% vs 2.9%; fatigue 10.5% vs 0%; raised ALT 5.3% vs 0%.	-	-

Estimated cost and cost impact

The cost of pemetrexed is £1,440 per cycle with additional costs of:

- Vitamin supplementation: approximately £7 per cycle.
- Cisplatin (during first line treatment for 4 cycles only): £67.77[34d] per cycle.

Claimed or potential impact – speculative

Patients

☑ Increased length of survival

☐ Reduction in associated morbidity or Improved quality of life for patients and/or carers

☐ Quicker, earlier or more accurate diagnosis or identification of disease

☐ Other:

☐ None identified

[d] Costings based on average weight 67.5kg (men and women) and average surface area 1.7m^2. Assumes wastage.

Services

☑ Increased use: new IV maintenance therapy	☐ Service organisation	☐ Staff requirements
☐ Decreased use	☐ Other:	☐ None identified

Costs

☑ Increased unit cost compared to alternative: induction therapy	☐ Increased costs: more patients coming for treatment	☐ Increased costs: capital investment needed
☐ New costs	☐ Savings:	☑ Other: new maintenance therapy

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, 90 Vincent Drive, Edgbaston, Birmingham, B15 2SP, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.haps.bham.ac.uk/publichealth/horizon