



Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in accordance with the licensed indication, based upon the evidence submission from the manufacturer (Eli Lilly) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The primary clinical outcome measure was progression free survival (PFS). Secondary outcomes included overall survival (OS), time to worsening of symptoms, objective tumour response rate, adverse events and changes in lung cancer symptom scale. Data for two populations were presented: patients with non-squamous NSCLC histology and patients with adenocarcinoma histology. The clinical evidence was derived from a double-blind, placebo-controlled randomised controlled trial (RCT), the JMEN trial. The trial compared the use of pemetrexed + best supportive care (BSC) as maintenance therapy, with placebo + BSC in patients with NSCLC ($n = 663$) who had received four cycles of platinum-based chemotherapy (CTX) and whose disease had not progressed. In the licensed population (patients with non-squamous histology), the trial demonstrated greater median PFS for patients treated with

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

pemetrexed than for patients in the placebo arm [4.5 vs 2.6 months; hazard ratio (HR) 0.44; 95% confidence interval (CI) 0.36 to 0.55, $p < 0.00001$]. Median OS was also greater for the pemetrexed-treated patients (15.5 vs 10.3 months; HR 0.70; 95% CI 0.56 to 0.88, $p = 0.002$). In addition, tumour response and disease control rates were statistically significantly greater for patients who received pemetrexed. Patient survival rates at 1 year and 2 years were higher in the pemetrexed arm. The incremental cost-effectiveness ratios (ICERs) estimated by the manufacturer's model were £33,732 per quality adjusted life-year (QALY) for the licensed nonsquamous population, and £39,364 per QALY for the adenocarcinoma subgroup. Both of these ICERs were above the standard NICE willingness-to-pay range (£20,000–£30,000 per QALY). The manufacturer also presented a case for pemetrexed to be considered as an end of life treatment. The ERG identified a number of problems in the economic model presented by the manufacturer; after correction, the base case ICER was re-estimated as £51,192 per QALY gained and likely to exceed NICE's willingness-to-pay thresholds. Following a revised economic analysis submitted by the manufacturer, the AC accepted that an ICER of £47,000 per QALY gained was most plausible. The AC also considered that maintenance treatment with pemetrexed fulfilled the end of life criteria. The guidance issued by NICE, on 20 June 2010, in TA190 as a result of the STA states that: People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.

1.1 Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled '*Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)*'.

Description of the underlying health problem

Lung cancer is the second most common cancer diagnosed in the UK, with over 33,000 new cases diagnosed in England and Wales in 2006, and the leading cause of cancer death.² Lung cancer is the second most common cancer in men after prostate cancer, and the third most common cancer in women after breast and bowel cancer.

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers diagnosed. The main subtypes of NSCLC are squamous cell carcinoma (33%), adenocarcinoma (25%), large cell carcinoma (4%), and NSCLC 'not-otherwise specified' (NOS; 36%).³ A further 1% are 'carcinoma in situ' and 1% are broncho-alveolar cell carcinoma. While cigarette smoking has been linked to all four types of lung cancer, the incidence of adenocarcinoma has been steadily increasing worldwide, and modifications to cigarette design are thought to be responsible for this shift in pathologic diagnosis pattern.⁴

Survival in patients with lung cancer is poor. It was responsible for approximately 29,600 deaths in England and Wales in 2007.² For patients with stage IIIB, only 7–9% may live for 5 years and for patients with stage IV (metastatic) cancer, only about 2–13% survive for 5 years.²

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages and advanced disease is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other

developed countries, is low active anti-cancer treatment rates. The National Lung Cancer Audit states that only 23.2% of NSCLC patients in England and Wales received first-line CTX in 2006.⁵

Maintenance treatment is a new treatment paradigm and is proposed as an alternative for the 'watch and wait' phase of the current treatment pathway, for patients with complete or partial response/stable disease after four cycles of first-line treatment.

The goal of maintenance treatment is to maintain the clinical benefit achieved with first-line CTX. Maintenance treatment is continued until disease progression.

Scope of the evidence review group report

Pemetrexed is licensed in Europe as monotherapy for the maintenance treatment of patients with NSCLC, other than predominantly squamous cell histology. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.⁶

The ERG report presents the results of the evaluation of the manufacturer (Eli Lilly) evidence submission regarding the use of pemetrexed as a maintenance therapy in the patient group outlined above. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer. The manufacturer submission (MS) described the use of pemetrexed + best supportive care (BSC) with BSC + placebo.

The primary clinical outcome measure was progression-free survival (PFS). Secondary outcomes included overall survival (OS), time to worsening of symptoms, objective tumour response rate, adverse events and changes in lung cancer symptom scale.

Cost-effectiveness was measured in terms of incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY).

Data for two populations were presented: patients with non-squamous NSCLC histology and patients with adenocarcinoma histology.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG evaluated the quality of the manufacturer's clinical effectiveness review. Searches conducted by the manufacturer were assessed for completeness, and the single trial put forward as evidence of effectiveness was critically appraised using the manufacturer's responses to specific questions in the submission template. With regard to cost-effectiveness evidence, the ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using a standard assessment tool,⁷ and conducted a detailed evaluation of the model. The ERG recalculated the base-case cost-effectiveness results, correcting a number of methodological errors and reanalysed the survival estimates. The ERG also undertook a basic probabilistic sensitivity analysis as this was not provided by the manufacturer.

Results

Summary of submitted clinical evidence

The evidence described in the MS is derived from a double-blind, placebo-controlled randomised controlled trial (RCT), the JMEN trial.⁸ The trial compared the use of pemetrexed + BSC as maintenance therapy, with placebo + BSC in patients with NSCLC ($n = 663$) who had received four cycles of platinum-based CTX and whose disease had not progressed. The MS focused on the clinical outcomes of the subgroup of patients with non-squamous histology ($n = 481$), which is the population for which pemetrexed is licensed in this indication; the MS also focused on a subgroup of the licensed population, patients with adenocarcinoma.

The results for the licensed non-squamous population are summarised in *Table 1*. In the licensed population the trial demonstrated greater median PFS for patients treated with pemetrexed than for patients in the placebo arm [4.5 vs 2.6

TABLE 1 Key results of the JMEN trial (non-squamous population)

End point	Pemetrexed (n = 325)	Placebo (n = 156)	HR (95% CI)	p-value
Primary				
PFS (months) median	4.5	2.6	0.44 (0.36 to 0.55)	<0.00001
Secondary				
OS (months) median	15.5	10.3	0.70 (0.56 to 0.88)	0.002
Tumour response (%) (CR + PR)	7.4	1.9		0.018
Disease control rate (%) (CR+PR+SD)	57.7	32.7		<0.001
Survival rate at 1 year (%)	60	42		
Survival rate at 2 year (%)	28	22		

CI, confidence interval; CR, complete response; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

months; hazard ratio (HR) 0.44; 95% confidence interval (CI) 0.36 to 0.55, $p < 0.00001$]. Median OS was also greater for the pemetrexed-treated patients (15.5 versus 10.3 months; HR 0.70; 95% CI 0.56 to 0.88, $p = 0.002$). In addition, tumour response and disease control rates were statistically significantly greater for patients who received pemetrexed. Patient survival rates at 1 year and 2 years were higher in the pemetrexed arm. The health-related quality of life (HRQoL) data presented were limited owing to high levels of censoring/missing data. Safety data demonstrated that patients treated with pemetrexed had statistically significantly higher rates of grade 3 or 4 neutropenia, and experienced higher rates of transfusions and hospitalisation due to drug toxicity.

Summary of submitted cost-effectiveness evidence

The manufacturer did not identify any published cost-effectiveness analyses of pemetrexed for the maintenance treatment of patients with NSCLC, and therefore developed a de novo economic model to support their economic case. The model compares pemetrexed + BSC with 'watch and wait' + BSC. The clinical data used in the economic model were primarily generated from the JMEN trial.⁸ Although the model was trial-based, there was also a modelling component to allow the extrapolation of health effects beyond the 29 month trial period up to 6 years. The manufacturer's economic evaluation adopts a lifetime horizon (taken as 6 years) for the consideration of costs and benefits, and the

perspective is that of the UK NHS and Personal Social Services.

The ICERs estimated by the manufacturer's model are £33,732 per QALY for the licensed non-squamous population, and £39,364 per QALY for the adenocarcinoma subgroup. Both of these ICERs are above the standard NICE willingness-to-pay range (£20,000–£30,000 per QALY).

The manufacturer also presented a case for pemetrexed to be considered as an end-of-life treatment.

Commentary on the robustness of submitted evidence

The manufacturer cited evidence from a well-designed trial (JMEN)⁸ of the clinical benefit of pemetrexed + BSC as maintenance treatment compared with placebo + BSC. The trial recruited a substantial number of patients in a difficult disease area. It is noteworthy that patients and assessors in the JMEN⁸ trial were blinded to treatment group allocation and that investigators' outcome assessments were independently verified.

The ERG noted that there was only one relevant RCT (JMEN)⁸ that compared pemetrexed + BSC as maintenance treatment with placebo + BSC. Despite designing the trial to include a comprehensive analysis of HRQoL, very limited data was collected and reported in the MS. This means it was very difficult to determine how patients' HRQoL would be affected by pemetrexed in a maintenance setting.

TABLE 2 Effect of corrections and amendments made by ERG to the manufacturer's model for the non-squamous population

Model amendment	Pemetrexed		Placebo		Incremental		Changes		ICER (£/QALY)	ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	Costs	QALYs		
Submitted base case	£17,455	0.9697	£8318	0.6988	£9137	0.2709	–	–	£33,732	–
All cycles of pemetrexed and revised CTX costs	£20,638	0.9841	£8323	0.6989	£12,315	0.2852	+£3178	+0.0143	£43,179	+£9447
Revised utility values	£17,455	0.9540	£8318	0.7057	£9137	0.2483	–	–0.0226	£36,798	+£3066
Continuity correction	£17,405	0.9467	£8288	0.6851	£9117	0.2615	–£20	–0.0094	£34,860	+£1128
Correct double discounting	£17,522	1.0006	£8352	0.7149	£9169	0.2857	+£32	+0.0148	£32,091	–£1641
Discounting assumptions	£17,421	0.9617	£8312	0.6909	£9109	0.2708	–£60	–0.0001	£33,640	–£88
Include monitoring costs	£17,838	0.9697	£8452	0.6988	£9386	0.2709	+£249	–	£34,651	+£919
Correct arithmetic	£17,398	0.9658	£8248	0.6953	£9149	0.2706	+£12	–0.0003	£33,817	+£85
Combined effect of above changes	£20,925	0.9539	£8370	0.6881	£12,555	0.2658	+£3418	–0.0051	£47,239	+£13,507
Combined effect of all changes including IPD survival analysis (excluding significant protocol violations)	£20,902	0.9851	£8382	0.7405	£12,520	0.2446	+£3383	–0.0263	£51,192	+£17,460

CTX, chemotherapy; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; QALYs, quality-adjusted life-years.

The primary end point of the key trial was changed by the manufacturer from OS to PFS during the course of the trial. No information was provided that fully justified the change of clinical end point.

The statistical analysis plan described by the manufacturer also included a test for treatment by histology interaction and corresponding subgroup analyses. The results for the subgroup of patients with non-squamous histology provided the clinical evidence in the MS. However, the trial randomisation process did not include stratification by histology status. Moreover, the restriction of the licensed population to only the non-squamous subgroup effectively reduced the statistical power of the trial, with consequences of increased uncertainty in the cost-effectiveness analysis.

The projection of survival from the end of the trial period, the costing of CTX treatment and the utility values used in the manufacturer's model were not ideal and underestimate the size of the ICER.

The manufacturer implemented a capping rule in its economic model to limit the maximum number of cycles of maintenance treatment that patients could receive. However, the cycle capping rule affected only costs; it did not take account of any reduction in outcomes caused by capping the maximum number of cycles at 17 rather than allowing the JMEN trial⁸ maximum of 55. Again, this capping rule underestimated the size of the ICER.

Making all of the necessary ERG corrections/adjustments to the manufacturer's model, the ERG's base-case ICER for the non-squamous population was estimated at £51,192 per QALY (Table 2).

Conclusions

The generalisability of the JMEN trial⁸ to UK clinical practice is uncertain for a number of reasons:

- None of the patients in the trial were recruited from the UK. A sizeable proportion (35%) of patients were from Asian countries; these patients are documented in the literature as having a better prognosis for NSCLC than other ethnic groups, and the Asian patients in the trial appear to have improved survival

times compared with patients of other ethnicities.⁹

- Patients in the trial were able to receive unlimited cycles of maintenance therapy. This is unlikely to be the case in clinical practice in England and Wales and it is unclear how this difference would impact on survival in a clinical setting.
- Paclitaxel was used in the JMEN trial as a first-line treatment for a greater proportion of patients in the trial than might be the case in clinical practice in England and Wales. The impact of this when generalising the results is unknown.
- A number of patients in the trial received second-line therapies that are not available to patients in clinical practice in England and Wales, which may have affected the OS observed in the trial.
- Confirmed histological diagnosis of non-squamous NSCLC is required before patients can be offered maintenance treatment with pemetrexed. While histological testing is routinely carried out in many centres in England and Wales, this will not be available to all patients. Therefore, it is unclear if pemetrexed for maintenance therapy will be available in all centres in the UK, which may give rise to equity concerns.

'End-of-life' criteria

Analysis of the JMEN trial⁸ individual patient data and revised projection modelling confirmed that the mean life extension from use of pemetrexed as maintenance therapy was likely to exceed 3 months. However, the number of patients who would be eligible to receive pemetrexed is uncertain. The manufacturer's estimates (used to present its end of life case) were based on amalgamation of information from different sources with differing definitions. The methods of calculation are not well reported and a number of assumptions were made which may not be valid.

Several factors serve to limit the generalisability of the trial to UK clinical practice, and the ERG could not be confident that the clinical results presented in the MS give a true reflection of the benefits that could be expected with pemetrexed for the maintenance treatment of patients with non-squamous NSCLC in UK clinical practice. Furthermore, in the economic analysis there were a number of problems identified with the model (in addition to the JMEN trial⁸ data) which indicate

that the ICER (re-estimated as £51,192 per QALY gained) could well exceed NICE's willingness-to-pay thresholds.

Summary of NICE guidance issued as a result of the STA

Following a revised economic analysis submitted by the manufacturer, the AC accepted that an ICER of £47,000 per QALY gained was most plausible. The AC also considered that maintenance treatment with pemetrexed fulfilled the end of life criteria. The guidance issued by NICE, on 20 June 2010, in TA190 as a result of the STA states that:

People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.

1.1 Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

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