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# Pemetrexed for the treatment of non-small cell lung cancer

## Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), evidence review group (ERG) report and personal statements made by nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

**The manufacturer was asked to provide the following information from the JMEI trial: further details of patient flow and survival statistics, 95% confidence intervals for the mean health-related utilities for adverse events, details of any analysis undertaken to explore the effects of crossover treatment, confirmation of the p value for the fixed-margin test (superiority hypothesis) and all explanatory variables contained in the Cox regression model.**

## Abbreviations

ALT    alanine transferase

BSC    best supportive care

BSA    body surface area

CI     confidence interval

DOC    docetaxel

ERG    Evidence Review Group

FDA    Food & Drug Administration

HR     hazard ratio

ICER   incremental cost-effectiveness ratio

ITT    intention to treat

MS     manufacturer's submission

NR     not reported

NSCLC  non-small cell lung cancer

PEM    pemetrexed

QALY   quality-adjusted life year

RCT    randomised controlled trial

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**Licensed indication under appraisal**

Pemetrexed (Alimta, Eli Lilly) is licensed as a monotherapy for treating patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

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# Key issues for consideration

## *Clinical effectiveness*

- The clinical experts believed pemetrexed should be made available to eligible patients who were allergic to docetaxel.

- The JMEI trial was a multicentre trial of pemetrexed compared with docetaxel conducted in 23 countries (not including the UK). The median patient age was 57 in the docetaxel arm and 59 in the pemetrexed arm. Patients with a performance status or 2 or more and those with sgnificant weight loss prior to enrollment were excluded. To what extent are the results of the JMEI trial generalisable to the wider UK NSCLC population?

- The manufacturer of pemetrexed states that clinically equivalent efficacy was demonstrated in the JMEI trial, however the ERG raised concerns about the methods of analysis of survival. Do the data demonstrate that pemetrexed is equally effective as docetaxel?

- In the JMEI trial, statistically significantly fewer patients randomised to pemetrexed experienced grades 3 and 4 neutropenia (neutropenia, febrile neutropenia and neutropenia with infection) compared with those taking docetaxel. The trial also found that statistically significantly fewer patients experienced alopecia in the pemetrexed arm, but more patients experienced raised ALT levels. There were no statistically significant differences in the other adverse events reported. There were no statistically significant differences between the treatment arms in disease-related quality of life. Does pemetrexed have a more favourable impact on adverse events and quality of life compared with docetaxel?

## *Cost effectiveness*

- The manufacturer's base-case analysis was not limited to the data from the JMEI trial, but was based on pooled estimates of absolute survival data from several trials. Was this approach to the analysis inappropriate?

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- Is the assumption that pemetrexed has a survival benefit compared with docetaxel used in the economic analysis appropriate?
- The manufacturer also included comparisons of pemetrexed with best supportive care (BSC). Are these comparisons appropriate?

# 1 Decision problem

## *1.1 Decision problem approach in the MS*

| Population | Adult patients with locally advanced/metastatic (unresectable) non-small cell lung cancer previously treated with chemotherapy. The number of prior chemotherapy regimens had to be at least one. |
|---|---|
| Intervention | Pemetrexed |
| Comparators | Docetaxel, erlotinib and best supportive care |
| Outcomes | Primary outcome<br>Overall survival<br>Secondary outcomes<br>Toxicities (including use of concomitant supportive measures)<br>Progression-free survival<br>Time to documented progressive disease<br>Time to treatment failure<br>Time to objective response<br>Duration of response<br>Quality of life measurements |

## *1.2 ERG comments on the manufacturer's submission*

### 1.2.1 **Population**

The ERG did not comment on the appropriateness of the population in the manufacturer's submission decision problem

### 1.2.2 **Intervention**

The ERG did not comment on the intervention in the manufacturer's submission decision problem.

### 1.2.3 **Comparators**

The manufacturer's submission contained evidence from RCTs comparing pemetrexed with docetaxel, erlotinib and BSC (also referred to as active

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supportive care). The ERG did not consider erlotinib to be an appropriate comparator as, although it is licensed for use in NSCLC, it is not currently approved in the UK for second-line use in patients with locally advanced or metastatic NSCLC and is not routinely used in clinical practice in England and Wales.

### 1.2.4    Outcomes

The primary outcome measures of the JMEI trial was overall survival of the ITT population. Secondary efficacy outcomes were progression-free survival, time to documented progressive disease, time to treatment failure, time to objective response, duration of response, quality of life measures and toxicities.  All these outcomes were deemed to be appropriate by the ERG.

## *1.3      Clinical specialists' and patient expert's statements*

The statements note that docetaxel has become the standard of care as second-line treatment for NSCLC. However, toxicity precludes the use of docetaxel in a majority of patients due to their poor performance status.

There are no specific disadvantages with pemetrexed compared with other chemotherapy agents in terms of toxicity and it will be tolerated by most patients without the need to reduce dosage. One of the experts suggested that pemetrexed would be a useful treatment option for eligible patients (i.e those with an adequate performance status) who are allergic to docetaxel. Some patients may prefer this treatment because of the lower rate of alopecia.

The patient expert submission emphasises that patients and their families place considerable importance on improving quality of life and small extensions in duration of life. The patient expert noted there are few active second-line treatment options available, so any new therapy offers patients much-needed hope.

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# 2 Clinical effectiveness evidence

## 2.1 Clinical effectiveness in the manufacturer's submission

**Direct comparison**

*2.1.1* The manufacturer's submission contained details of one trial which investigated the effectiveness of pemetrexed within its licensed indication compared with docetaxel (the JMEI trial)The trial was an open-label RCT (n = 571), with a median follow-up period of 7.5 months. Participants received pemetrexed 500 mg/m$^2$ with vitamin B$_{12}$, folic acid and dexamethasone or docetaxel 75mg/m$^2$ with dexamethasone. The main results are summarised below.

2.1.2 The original study sample size was based on a hypothesis of superiority of pemetrexed compared with docetaxel (hazard ratio [HR] greater than 1.00), with 85% power and a 0.05 level of significance. The protocol was amended to test for non-inferiority using the fixed-margin method. Non-inferiority was assumed to be confirmed if the overall survival was less than or equal to 10% worse among participants receiving pemetrexed (upper band of the 95% confidence interval [CI] less than 1.11).

2.1.3 The protocol was also amended to test for non-inferiority using the percentage of efficacy retention method (Rothmann method). The manufacturer stated this was because 'the fixed margin method does not consider the variability from the historical trial of control treatment compared with the historical control' (see manufacturer's submission, section 2.5). The analysis assumed that pemetrexed must retain 50% of the survival benefit of docetaxel in order to be deemed equally effective. The estimate of the effectiveness of docetaxel is taken from the TAX317 trial which compared docetaxel with BSC (HR 0.56; 95% CI, 0.35 to 0.88). Table 1 shows that pemetrexed retained 102% (95% CI 52% to 157%) of the survival benefit of docetaxel over BSC when analysed in this way.

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**Table 1 Overall survival**

| Trial | Intervention (median, months) | Comparator (Median, months) | Hypothesis | Result | 95% CI | p value |
|---|---|---|---|---|---|---|
| JMEI | PEM (8.3) | DOC (7.9) | Superiority HR > 1.00 | NR | NR | 0.93 |
| JMEI | PEM (8.3) | DOC (7.9) | Non-inferiority HR < 1.11 | 0.99 | 0.82 to 1.20 | 0.226 |
| JMEI /TAX317 | PEM (8.3) | DOC vs BSC TAX317 trial (NR) | Pemetrexed retains at least 50% of survival benefit of docetaxel vs BSC) | 102% | 52% to 157% | 0.047 |
| BSC, best supportive care; CI, confidence interval; DOC, docetaxel; HR, hazard ratio; NR, not reported; PEM, pemetrexed. | | | | | | |

2.1.4    There were no statistically significant differences between the pemetrexed and docetaxel groups in terms of progression-free survival, time to progressive disease, duration of tumour response, duration of clinical benefit and time to objective tumour response. Patients randomised to pemetrexed had a statistically significantly longer time to treatment failure than docetaxel (HR = 0.84; 95% CI, 0.71 to 0.997), although the absolute difference was small (pemetrexed median 2.3 months; docetaxel median 2.1 months).

2.1.5    Of the grades 3 and 4 haematological toxicities, pemetrexed was associated with statistically significantly less neutropenia ($p < 0.001$), febrile neutropenia ($p < 0.001$) and neutropenia with infection ($p = 0.004$). No statistically significant differences were found for anaemia (or number of patients receiving red blood cell transfusions or erythropoietin) or thrombocytopenia. No statistically significant differences were reported for 10 of the 12 non-haematological toxicities reported. Patients randomised to pemetrexed experienced statistically significantly less alopecia ($p < 0.001$) but more raised levels of alanine transferase (ALT) ($p = 0.028$).

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2.1.6    Pemetrexed was associated with statistically significantly fewer hospitalisations for neutropenic fever ($p < 0.001$) and uses of granulocyte colony-stimulating factor ($p < 0.001$). No statistically significant differences were reported for rate of hospitalisations for any other drug-related adverse event ($p = 0.092$). Further details are provided in pages 77–79 of the manufacturer's submission.

2.1.7    No statistically significant differences were found in disease-specific quality of life, measured using the Lung Cancer Symptom Scale, which includes six symptoms (anorexia, fatigue, cough, dyspnoea, haemoptysis and pain).

## 2.2    ERG comments

2.2.1    The ERG stated that they agreed with the views expressed by the US Food and Drug Administration (FDA) who said 'The study (JMEI) …failed to demonstrate efficacy based on the fixed-margin non-inferiority test as defined in the amended protocol … [and] based on the FDA analysis the study failed to demonstrate efficacy based on the percent retention of control effect non-inferiority testing'(see section 2.1.3).

2.2.2    The ERG noted that the open-label design of the trial may have introduced bias in the measurement of subjective outcomes such as quality of life.

2.2.3    The ERG noted that the statistically significant difference in time to treatment failure represented an absolute difference of 6 days and that there were differences in some measures of toxicities. It also noted that these differences did not translate into differences in quality of life.

## 2.3    Clinical specialists' and patient experts' statements

2.3.1    A clinical specialist noted that there were similar survival estimates in all of the three key trials of second-line treatments for NSCLC.

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2.3.2      Participants were approximately 10 years younger than the median age of patients diagnosed with NSCLC in all these key trials.

2.3.3      A clinical specialist noted that people with good performance status who responded to previous treatment are most likely to benefit from pemetrexed and docetaxel. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 were excluded from the JMEI trial.

2.3.4      A clinical specialist noted that quality of life is regarded as a supplementary reason to give second-line chemotherapy for NSCLC and that response correlates closely with improved quality of life. A much greater number of participants were assessed for quality of life in the JMEI trial than the other trials, but there was no clear difference between docetaxel and pemetrexed.

# 3      Cost-effectiveness evidence

## 3.1      *Cost effectiveness in the manufacturer's submission*

3.1.1      The company submitted a Markov model, with the three main health states being defined as response, stable, and progressive disease. The model was designed to compare pemetrexed with docetaxel and BSC. The model included a range of adverse events.

3.1.2      The survival estimates in the base-case analysis were based on a pooled analysis of absolute survival from the treatment arms of several studies.

See from page 96 of the manufacturer's submission for a description of the model, and pages 34–50 of the ERG report for a summary and critique.

**Table 2**
The base-case results of the manufacturer's economic analysis

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| Comparison | Incremental QALY | Incremental cost | ICER |
|---|---|---|---|
| Pemetrexed vs docetaxel | 0.07 | £1,375 | £18,672 |
| Pemetrexed vs BSC | 0.21 | £3,379 | £16,458 |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year | | | |

## *3.2    ERG comments*

3.2.1    The ERG stated that the survival estimates used in the model were not based on a direct head to head comparison of pemetrexed vs docetaxel but were based on a pooling methodology that could not be considered reliable or meaningful. The ERG also noted other limitations and performed a crude adjustment to the results to counter them.

3.2.2    The ERG noted the following limitations of the manufacturer's economic model.

- Patients can only experience side effects in the stable and responding health states.
- Responding patients cannot move to a stable health state.
- Side effects appear to be restricted to treatment-related events.
- Death only occurs in the progressive health state or for patients experiencing febrile neutropenia.
- Patients can only die of cancer or treatment-related causes.
- Patients cannot die in the first cycle of treatment.

3.2.3    The ERG assumed there is no overall survival difference between pemetrexed and docetaxel based on the findings of the JMEI trial. This change alone to the submitted model resulted in an incremental cost-effectiveness ratio (ICER) of £458,333 per additional quality-adjusted life year (QALY) gained.

3.2.4    In addition to amending the survival estimate, the ERG made the following amendments to the manufacturer's analysis.

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- Pemetrexed and docetaxel dosing: the manufacturer's submission assumed all patients would have a body surface area of 1.7m$^{2.}$. The ERG assumed that body surface area would follow a normal distribution with a  mean of 1.83m$^2$. As a result the ERG estimated that a greater number of pemetrexed vials would be required.

- Chemotherapy cycles: the ERG estimation was based on the results of the JMEI trial rather  than the number included in the manufacturer's submission.

- Drug administration costs: NHS reference and tariff costs were used to estimate drug administration costs

- Transport costs: The ERG also included cost of patient transportation to and from the chemotherapy centre for patients receiving chemotherapy as in-patients.

- Adverse event costs: The ERG used an alternative sources for the unit of treating febrile neutropenia.

- Palliative care costs: The ERG assumed there was no difference in palliative care costs between pemetrexed and docetaxel.

These amendments resulted in an ICER of £1.18 million per QALY qained.

### 3.2.5    Key conclusions

- Pemetrexed  would only be cost effective if an overall survival benefit were to be assumed.
- The most influential factor (apart from the estimate of efficacy) in the economic model is the estimation of the number of cycles of chemotherapy required.

## *3.3    Technical Lead/Technical Adviser comments*

3.3.1    Most of the criticisms of the MS economic model would also apply to pemetrexed vs BSC, but the trials included  people with a performance status of 2, so there would be a greater survival benefit for pemetrexed in this specific evaluation.

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3.3.2    The manufacturer's base-case economic analysis was based on the pooling of survival data from several studies. An indirect comparison was also conducted as a sensitivity analysis. It is not clear if the data for the indirect comparison were based on absolute or relative treatment effects. The mean ICER of pemetrexed compared with docetaxel using the indirect comparison was £31,612 per QALY (see the manufacturer's submission, page 141).

3.3.3    The mean ICER of pemetrexed compared to BSC using the indirect comparison was £10,298 in the manufacturer's submission. None of the analysis of cost-effectiveness of pemetrexed vs (BSC or docetaxel) was based on a head to head comparison.

# 4    Authors

Helen Tucker (Technical Lead) and Louise Longworth (Technical Adviser), on behalf of the Committee Chair (Andrew Stevens) and the Lead Team (Peter Clark and Peter Jones).

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