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Pemetrexed for the maintenance treatment of non-small-cell lung cancer
Lilly response to the Appraisal Consultation Document (ACD)

Dear Carole

Thank you for forwarding the Appraisal Consultation Document (ACD) on pemetrexed for the maintenance treatment of non-small cell lung cancer (NSCLC), and for the opportunity to comment on the ACD.

Pemetrexed as maintenance therapy is a well-tolerated medicine that provides a significant step-change in the treatment of patients with advanced non-squamous NSCLC who have not progressed with first-line therapy by extending median survival by more than five months, compared to best supportive care only, the current standard of care. An increase in survival of over five months and median overall survival of approximately 18 months from start of chemotherapy are unprecedented benefits for patients with advanced NSCLC.

Lilly are pleased that the Committee concluded that the evidence submitted by the manufacturer was robust enough to show that maintenance treatment with pemetrexed fulfilled the supplementary advice from NICE for appraisal of treatments which extend lives of patients with otherwise short life expectancy and which are licensed for indications that affect a small number of patients.
However, we are concerned that the Appraisal Committee did not recommend pemetrexed for maintenance therapy in their preliminary decision even when the end of life criteria, intended to improve access to medicines for patients with terminal conditions, are taken into consideration.

Our key comments are on the following topics:

Impact of treatment duration on the uncertainty around the cost-effectiveness estimate.

Duration of therapy for the maintenance treatment of NSCLC is not established as it is a new option of clinical care in NSCLC. At this stage it is difficult to anticipate the most appropriate

duration for therapy to accomplish the maximum benefit from pemetrexed. In the pivotal clinical trial (JMEN), the majority of patients received a maximum of up to 15-20 cycles of treatment and the median number of cycles in the non-squamous patient population was 6.

Furthermore, around 10% of patients received more than 17 cycles (i.e. 1 year of treatment) and less than 5% received more than 35 cycles (i.e., 2 years of treatment). Only one patient received 55 cycles. The approach followed by Lilly in the submitted economic model was an attempt to reflect the most likely scenario of expected clinical practice based on the distribution observed in the JMEN trial.

In response to the discussion around treatment duration for pemetrexed in maintenance, Lilly have performed additional scenarios in the economic model adjusting costs and benefits at different treatment durations: 1 year, 2 years and duration as seen in the JMEN trial. The results obtained show that the ICERs are most likely to vary between £46,000 and £49,000.

Application of end of life supplementary advice

- Principles of end of life criteria

The end of life criteria together with other recent developments in pharmaceutical and industrial policy such as the Kennedy Report, advocate for NICE to have a broader perspective and more pragmatic approach when assessing new medicines.
In line with the NICE Citizens Council and the NICE social value judgements, other factors such as: severity of disease, terminal illness, and medicines where cost of treatment may far outweigh best supportive care, should be taken into consideration in the decision making process.

This is particularly the case in the assessment of end of life treatments where medicines that extend life are penalised for keeping patients alive and that are unlikely to ever be cost-effective under the traditional ICER thresholds. The use of a standard higher cost per QALY threshold as the key decision making factor for end of life treatments will miss out on the overall value of these products.

- The size of QALY weight to be considered for acceptable current threshold range.

Despite the recognition of the significant clinical value of pemetrexed and the application of the supplementary advice, the Committee concluded that the size of the additional weight that would need to be assigned to the QALY benefits for the ICER to fall within the current threshold range would be too great to be cost-effective even considering the supplementary advice.

Although NICE has not provided an explicit upper threshold for end of life treatments, a Committee has already approved treatments with a de facto QALY weight of 1.7 (i.e. upper limit of £50,000/QALY). In the case of sunitinib for the treatment of renal cell carcinoma (RCC), the Committee concluded that '*although it might be at the upper end of any plausible valuation of such benefits, in this case there was a significant step-change in treating a disease for which there is only one current standard first-line option*". We believe pemetrexed as a maintenance treatment offers a similar step-change for patients with advanced non-squamous NSCLC.

The new cost-effectiveness estimates provided for various scenarios (see Appendix 2), consistently fall within the ICER range that NICE appears to have considered acceptable in prior appraisals subject to the end of life supplementary advice, of values of about £50,000/QALY. At present the cost-effectiveness of pemetrexed without a patient access scheme is in the same range as sunitinib with a patient access scheme. Therefore, pemetrexed should be considered

even more cost-effective since it does not have the burden of managing a patient access scheme within the NHS.

More detailed feedback on the application of the end of life supplementary advice is provided in Appendix 1.

Small patient population leading to limited budget impact for the NHS.

The eligible population for maintenance treatment is very small as only a subgroup of those receiving first-line therapies will be suitable for maintenance treatment (n=949 across England and Wales, MS submission Section 6.4, Table 9). The eligible population will decrease in size as pemetrexed first-line becomes standard of care in non-squamous NSCLC patients (NICE TA181) as pemetrexed maintenance therapy is not licensed for use following first-line pemetrexed treatment. According to the cycle distribution in the clinical trial, the proportion of patients likely to receive more than 17 cycles (about 10%) would translate to less than 100 patients in England and Wales. The number of patients being treated beyond two years would translate to less than 5%, fewer than 50 patients.

Therefore, only 7 patients per PCT (considering 147 PCTs in England) would be eligible for maintenance treatment with less than one patient per PCT going beyond one year of treatment. Taking the small number patient population into consideration and the average treatment cost per patient of approximately £12,076 the overall impact of introducing pemetrexed into the NHS is relatively small.

Issues with Patient Access Schemes

Although manufacturers of other oncology drugs appraised under the end of life criteria have proposed patient access schemes to allow patients to have access to new treatments, the approval, implementation and monitoring of patients under such schemes is very burdensome to the NHS and the manufacturer. NHS customers and the Department of Health (DH) believe '*the proliferation of schemes is creating an unnecessary burden to the NHS*' and consider '*they should be the exception not the norm*'.

As patient access schemes have the potential to be administratively burdensome with a danger that the extra workload will fall on clinical staff, it is not considered appropriate or helpful to introduce a patient access scheme within the context of increasing NHS productivity, when the eligible population for pemetrexed as maintenance treatment is so very small.

Conclusions

- Pemetrexed as maintenance therapy represents a step-change in the therapeutic approach to advanced non-squamous NSCLC.
- Pemetrexed is a well tolerated medicine that increases survival by more than five months, an unprecedented benefit for patients with advanced NSCLC.
- The new cost-effectiveness results are consistently below or around £50,000 per QALY irrespective of treatment duration.
- The ICER values (without a patient access scheme) are in line with other products already approved under the end of life criteria. The additional burden and cost of implementing patient access schemes in the NHS should be taken into consideration in the decision making process.
- This is even more so, if we consider that the estimated number of patients that will be eligible for treatment following first-line treatment is likely to be small, given that pemetrexed is fast

becoming the new standard for first-line treatment, and pemetrexed maintenance is not indicated for use after first-line pemetrexed.

We also enclose in Appendix 2 our response to points raised by the Appraisal Committee and the ERG in relation to the economic model.

In Appendix 3 we include a table with observed factual inaccuracies in the ACD.

Pemetrexed represents a new well tolerated option of treatment for patients with advanced non-squamous NSCLC that significantly increases survival in a challenging terminal disease. We hope that the above information will enable NICE to recommend, as an option of care, pemetrexed in the maintenance treatment of patients with advanced non-squamous NSCLC.

Yours sincerely

[redacted] **Lilly UK**

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Appendix 1 - Application of End of Life supplementary advice: size of QALY weight to be considered for acceptable current threshold range.

Lilly are pleased that the Committee concluded that the evidence submitted by the manufacturer was robust enough to show that maintenance treatment with pemetrexed fulfilled the supplementary advice from NICE for appraisal of treatments which may extend lives of patients with otherwise short life expectancy and which are licensed for indications that affect a small number of patients.

Despite the recognition of the significant clinical value of pemetrexed and the application of the supplementary advice, the Committee has made a preliminary decision not to recommend the use of pemetrexed as maintenance therapy in NSCLC. The Committee concluded that the size of the additional weight that would need to be assigned to the QALY benefits for the ICER to fall within the current threshold range would be too great to be cost effective even considering the supplementary advice.

Lilly notes that in a recent NICE appraisal of sunitinib under the end-of-life criteria, the ERG adjusted the manufacturer's ICER to £54,400/QALY as reported in the ACD and the Final Appraisal states that the Committee was persuaded that the ICER could be less than £50,000 per QALY gained.

The Committee are quoted as "*the committee concluded that although it might be at the upper end of any plausible valuation of such benefits, in this case there was a significant step-change in treating a disease for which there is only one current standard first-line option*".

Lilly are concerned that a current threshold ICER range of around of £50,000/QALY is referred to in the appraisal of a treatment fulfilling the end of life criteria. Although the "Update report on the application of the 'End of Life' supplementary advice in health technology appraisals" states that the Committee has *de facto* accepted a highest weight of 1.7 relative to £30,000, the supplementary advice does not give any specific guidance as to what constitutes an acceptable additional QALY weight and therefore an acceptable threshold to positively recommend a new treatment.

The end of life criteria were conceived in order to provide better access to medicines for patients with short life expectancy, giving NICE more flexibility in their assessment of new treatments by encouraging a broader and more pragmatic approach taking into consideration other factors such as disease severity and lack of alternative active treatments. The supplementary advice, together with other recent developments in the pharmaceutical and industrial policy (i.e. Kennedy report and OLS) acknowledge the role and responsibility of NICE in recognising the potential for long terms benefits to the NHS of innovation and in supporting the development of new treatments that are anticipated to be licensed for small groups of patients with terminal illnesses.

The use of an implicit higher cost per QALY threshold as the main criteria for recommending new treatments does not fully capture the overall value that the medicine may provide to patients with that condition and the NHS as a whole.

Lilly believe the situation with pemetrexed is fairly similar to that of sunitinib in that while pemetrexed represents an incremental step change to the treatment of advanced NSCLC, it is a novel indication for which at present only best supportive care is available.

In summary, pemetrexed represents a clinical innovation in the treatment of advanced NSLC and it is a novel indication for which at present only best supportive care is available. Therefore Lilly hopes that the Appraisal Committee will reconsider its decision.

Appendix 2 - Economic assumptions

Although, the Appraisal Committee has recognised the clinical value and the tolerability aspects of pemetrexed as maintenance therapy for non-squamous NSCLC, the Committee questioned some of the assumptions used in the economic model that underpin the most likely range of cost per QALY for pemetrexed.

In particular, the Committee's preliminary decision not to recommend pemetrexed in maintenance phase appears to be based on the following concerns:

a) Treatment duration - Normalisation of skewed distribution to a maximum of one year of treatment (17 cycles) to reflect expected clinical practice, with no similar adjustment to survival benefits
b) Differential utilities assigned to patients by treatment arm at initiation prior to any potential benefit of active therapy
c) The absence of Probabilistic Sensitivity Analysis (PSA) to explore uncertainty around the base-case ICER

a) Treatment duration in UK clinical practice: normalisation of costs and benefits of JMEN data

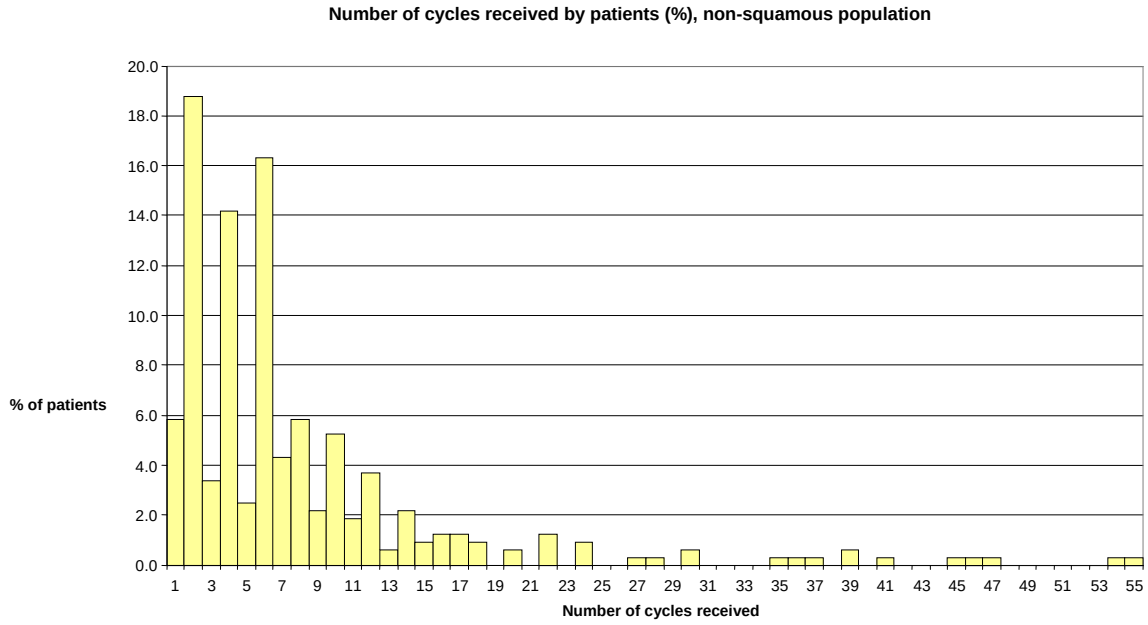
In JMEN, patients continued to receive treatment until their disease had progressed. As can be seen from the distribution of cycles in Figure 1 the majority of the patients (89-93%) received no more than 15-20 cycles of treatment; only 10% received more than 17 cycles (i.e., 1 year of treatment); and less than 5% received more than 35 cycles (i.e., 2 years of treatment). The median number of cycles was 6. Only one patient received 55 cycles. This led to a cycle distribution that was highly skewed to the right. The normalisation of cycles in the economic model at a maximum of 17 cycles was an attempt to model the most likely scenario based on the distribution from the JMEN trial.

The clinical specialist advising NICE on this topic states, as captured in the ACD, that JMEN is likely to reflect UK clinical practice i.e. patients will be treated until disease progression. However, it is not necessarily likely that patients would continue for such a prolonged period (for a very small number of patients) as observed in the clinical trial. In line with this (and consistent with feedback from clinical experts consulted by Lilly who suggested 10 cycles as a likely maximum), the ERG in their report state that although patients in JMEN could receive unlimited cycles of maintenance therapy, this is unlikely to be the case in clinical practice in England and Wales..

Since maintenance therapy for NSCLC is a new concept in the UK treatment duration in clinical practice is currently not well defined. Pemetrexed is licensed for use until disease progression and is also well-tolerated so physicians may choose to continue therapy; however the actual number of patients receiving more than one and two years of pemetrexed is likely to be very small. The median time to progression was 4.5 months in the clinical trial for the non-squamous population (corresponding to the median of 6 cycles reported above). The eligible population for maintenance treatment is already small as only a subgroup of those receiving first-line therapies will be licensed and appropriate (in terms of tumour response and performance status) for maintenance treatment (n=949 patients in England and Wales). This number is likely to decrease as pemetrexed becomes a standard of care (NICE TA181) for first-line treatment, thus reducing the number of patients who might receive pemetrexed maintenance as it is not indicated after exposure to pemetrexed in the first line setting.

In the light of the discussion around duration of treatment, Lilly have performed additional scenario analyses with the economic model to provide an overview of the variability of the ICER adjusting for overall survival and costs based on maximum treatment of t 1 year (17 cycles), 2 years (35 cycles) or as observed in the JMEN trial (maximum of approximately 3 years). For the analyses with maximum of 17 or 35 cycles, cycle and survival data from patients who exceeded these limits were excluded, respectively. The survival distribution parameters at one and two years and the results from the scenario analyses are provided in Tables 3 and 4 below, respectively. We believe these analyses better capture the normalisation of costs and adjusted survival and therefore provide greater certainty around the estimates of cost-effectiveness of pemetrexed in maintenance compared to best supportive care.

Figure 1. Distribution of maximum number of cycles of pemetrexed in JMEN trial



b) <u>Differential utilities assigned to patients by treatment arm at initiation</u>

The Committee discussed the utility values used by Lilly in the submitted economic model and the appropriateness of assigning differential utility values for patients entering the model who were in the same clinical state (without disease progression) and also felt that these values did not take account of disutility from adverse events.

The univariate sensitivity analysis that was included in the submission demonstrated that the differential utility values in the economic model are not a key driver. In the new scenarios for the economic model presented at the end of this Appendix, Lilly has taken into consideration a conservative approach to the utilities (i.e. same utilities applied to both arms and ERG assumptions) in line with the conclusions stated in the ACD, which show again that utility values are not a key driver in the overall analyses or in the PSA..

The ERG also noted that the disutilities of adverse events associated with pemetrexed were not considered in the submitted base case. In light of the good tolerability profile of pemetrexed and the

results from the JMEN study, which showed that no grade 3/4 toxicity had an incidence >5% and that less than 10% of patients discontinued therapy due to toxicity, Lilly believe that the impact on the ICER of the disutility associated with toxicities would be minimal. Although the rates of grade 3/4 toxicities in the pemetrexed arm were statistically significantly greater than the control arm, one must consider that the control was no active therapy and that absolute toxicity rates were low. In addition, it is likely that the disutilities associated with side effects of chemotherapy are balanced by the palliative effect on symptoms such as pain.

c) <u>The absence of PSA to explore uncertainty around the base-case ICER</u>

The Committee raised concerns that Lilly had not address the uncertainties in the model around the base case ICER with PSA. In order to address this concern Lilly have performed a PSA in accordance with the NICE methods guide. Below we describe the variables and the associated distributions used to run the PSA. The PSA has been produced by running 10,000 Monte Carlo simulations.

Utility values

The regression output in Table 2 of Nafees *et al* 2008 has been used to characterise the uncertainty in the utility values taken from that source. Normal distributions were assigned to the regression parameters as this is the appropriate distribution for coefficients estimated in a regression framework. As the covariance matrix was not reported it was not possible to reflect correlation.

There was no information on the variance of the utility estimates sourced from Berthelot *et al,* 2000. An assumption was made to utilise the standard error associated with the 'Progressive' health state from Nafees *et al*. This could be considered to underestimate the uncertainty given that the values in Berthelot et al were derived from expert opinion, but is consistent with the other utility values utilised in the model. Beta distributions were assigned to the utility values sourced from Berthelot *et al,* 2000.

Table 1: Mean and Standard errors of utility values

	Mean	Standard error
Stable disease (intercept)	0.6532	0.02223
Response	0.0193	0.006556
Progressive	-0.1798	0.02169
Fatigue	-0.07346	0.01849
Nausea/vomiting	-0.04802	0.01618
Anaemia*	-0.07346	0.01849
Neutropenia	-0.08973	0.01543

** Anaemia values were assumed to be the same as for fatigue*

In the scenarios that assign disutility for adverse events to the pemetrexed arm, distutility values and standard errors were weighted by the incidence of the adverse events.

Treatment Duration (number of cycles)

The mean number of cycles of pemetrexed matches that calculated by normalising the distribution of number of cycles at a maximum of 17, 35 and the JMEN trial duration depending on the scenario being considered. The mean number of cycles of placebo matches that observed in the trial in the latter scenario, but is re-calculated in the scenarios with a maximum of 17 or 35 cycles. The standard errors for both treatments are calculated from the standard deviations and number of participants for each scenario. Lognormal distributions were used to characterise uncertainty in the number of cycles as this is consistent with the right-skewed distribution of cycles observed in the trial.

Table 2: Mean and Standard deviations for different treatment duration

	Pemetrexed		Placebo	
	N	**Mean (std dev)**	**N**	**Mean (std dev)**
17 cycle maximum	298	5.8 (3.89)	151	3.7 (2.35)
35 cycle maximum	315	6.8 (5.68)	155	4.3 (4.15)
Trial-based	325	8.0 (8.62)	156	4.5 (5.32)

Adverse events

Beta distributions were used to characterise uncertainty in the rate of adverse events. Data on the number of events out of the total sample size were used directly to determine the alpha (number of events) and beta (total sample size less the number of events) parameters.

Overall survival

The probabilistic analysis is based on the parameterised estimates of overall survival for all six years (i.e. those recorded in B20:J20 on the 'Results' sheet). The observed data on survival are not utilised in the probabilistic analysis. Different exponential parameters (intercept and standard error) were used for the different trial durations assessed in the scenario analyses. The Cholesky decomposition of the covariance matrix is used in combination with standard normal random variates to generate correlated random draws of the intercept and scale parameter from the Weibull regressions (equivalent to assuming that the intercept and scale parameter are drawn from a multivariate normal distribution). A normal distribution is used to characterise uncertainty in the intercept from the Exponential regressions.

Results of the Scenario Analyses in the Economic Model

Lilly have addressed the concerns mentioned above by performing new scenario analyses that take into consideration these factors by

a) adjusting the overall survival in conjunction with duration of therapy for patients who received a maximum of one year, two years or duration as observed in the trial.

b) applying the same or more conservative adjustment to utilities and,

c) providing PSA around the ICER estimates.

Table 4: Scenario analyses adjusted to address Committee concerns

Scenario	Utility	Overall Survival	Number of cycles	ICER	PSA (lambda £50K)
Scenario 1	0.663 placebo 0.657 pem (as reported in ERG's base case)	Patients who received up to1 year/17 cycles	1 year/ 17 cycles (mean 6 cycles)	£49,105	50%
Scenario 2	Same utility applied both arms (0.66)	Patients who received up to1 year/17 cycles	1 year/17 cycles (mean 6 cycles)	£47,656	55%
Scenario 3	0.663 placebo 0.657 pem (as reported in ERG's base case)	Patients who received up to 2 years/35 cycles	2 years/ 35 cycles (mean 7 cycles)	£50,286	46%
Scenario 4	Same utility applied both arms (0.66)	Patients who received up to 2 years/35 cycles	2 years/ 35 cycles (mean 7 cycles)	£48,897	51%
Scenario 5	0.663 placebo 0.657 pem (as reported in ERG's base case)	Trial population (unadjusted)	Trial (mean 8 cycles)	£46,750	56%
Scenario 6	Same utility applied both arms (0.66)	Trial population (unadjusted)	Trial (mean 8 cycles)	£46,137	58%

Cost of pemetrexed has been adjusted based on Body Surface Area (BSA) of 1.8m^2 in light of comments from the ERG in all scenarios. The minor model error identified by the ERG has also been corrected.

The results presented in Table 4 above show that all the ICERs are approximately £50,000 per QALY and are consistent at different treatment duration. The probability of being cost effective at the implicit cost per QALY threshold of £50,000 used in the ACD is 55%, 51% and 58% at one year, two years and trial duration, respectively for the scenario where same utility values are applied to both arms.

Overall survival and treatment duration are strongly associated in the trial and the economic model; this is shown by the consistency of the ICERs in the different scenarios. Since the Committee has acknowledged the clinical value and the robustness of the survival data, this should as a result reduce the uncertainty around the base case ICER.

Appendix 3. Factual inaccuracies in the ACD

ACD Section	Current text	Description of erratum	Amendment required
3.1	The manufacturer's submission contained evidence on clinical effectiveness of pemetrexed maintenance therapy compared with best supportive care.	Patients in JMEN received either pemetrexed plus best supportive care or placebo plus best supportive care. Patients in both treatment arms received best supportive care.	The text should be amended to accurately describe the treatment clinical trial design.
3.3	There were few extreme outliers who received more than 20 cycles, up to 55 cycles in certain cases (7–11% of participants received more than 20 cycles).	Only 1 patient received up to 55 cycles	The text should be amended as follows: "There were few extreme outliers who received more than 20 cycles, up to 55 cycles in one case (7–11% of participants received more than 20 cycles)."
3.4	The manufacturer's submission noted the absence of trial-based health-related quality-of-life data because many of the participants failed to complete quality-of-life surveys.	The manufacturer's submission stated that a high rate of censoring for time to worsening of symptoms analysis may be due to high rate of non-completion at the post-discontinuation assessment which was expected to coincide with "worsening". However, completion of quality-of-life surveys while patients were on therapy was high (90%); 91% pemetrexed, 86% placebo.	The text should be amended accordingly.
3.8	Although this resulted in patients receiving up to 55 cycles in certain cases….	Only 1 patient received up to 55 cycles	The text should be deleted OR 'this resulted in one patient receiving up to 55 cycles…'
3.9	In absence of date on health-related quality of life from the JMEN trial,....	The health-related quality-of-life instrument used in the trial (ie, LCSS) focuses on disease symptoms and is not a preference-based instrument.	The text should be amended as follows: 'In the absence of preference-based health-related quality of life data..'
3.11	Most of the results in the one-way sensitivity analyses had little effect on the base-case ICERs. However, two results did have a large effect.	Three results had large effect. When the incremental survival of pemetrexed was increased from 5.3 months in the base case to 9.9 months, the ICER decreased to £20,680 per QALY gained	The text should be amended appropriately.
3.13	The ERG noted that the inclusion criteria of the JMEN trial were restricted to younger	The inclusion/ exclusion criteria for JMEN did not specify an upper age limit.	This text should be deleted.

	patients		
3.14	It considered that this decision had the effect of truncating the data available for analysis of overall survival, which is of critical importance to the economic evaluation.	Despite change in primary endpoint, analysis of OS was conducted as previously defined with retention of statistical power. Patients were followed until a sufficient number of events (deaths) had occurred.	This text should be deleted.
3.14	The ERG considered the high rate of missing data on health-related quality of life to be a limitation. It was not clear how patients' quality of life would be affected by maintenance treatment with pemetrexed.	High rate of non-completion at post-discontinuation assessment limited the time to worsening analysis. However, high rate of completion while patients were on therapy (90%). Lack of 'worsening' events suggests that quality of life is maintained while on therapy. Sensitivity analyses that varied the threshold of "worsening" yielded similar results.	The text should be amended accordingly.

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