NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous NSCLC

Response to consultee, commentator and public comments on the second and third Appraisal Consultation Documents (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee / Document	Comment	Response
Lilly UK – ACD2	Pemetrexed continuation maintenance treatment is a valuable treatment option that enables patients to maintain the benefit of first-line standard of care treatment for non-squamous NSCLC, further extending their overall survival (OS) and improving 1- and 2-year survival rates. In the pivotal maintenance trial PARAMOUNT, pemetrexed-treated patients experienced a median overall survival (OS) of 13.86 months compared with 11.01 months for patients receiving placebo (Paz-Ares et al. 2013). This translates to a mean survival gain in excess of 3 months in the lifetime economic model. One and two-year survival rates in pemetrexed-treated patients were significantly higher at 58% and 32% respectively compared to 45% and 21% in the placebo arm.	Comments noted.
Lilly UK – ACD2	Our response focuses mainly on the key aspects of the technology appraisal as discussed by the Committee, i.e. the cost-effectiveness case for pemetrexed, its consideration under the 'End of Life' supplementary criteria and the ethical implications of the negative guidance.	Comments noted.
Lilly UK – ACD2	Lilly strongly believes the ERG's alternative approach to modelling is inappropriate and biased against pemetrexed. In these circumstances we are concerned that it was not adequately scrutinised by the Committee. We present our concerns with the ERG's modelling approach and address the Committee's concerns regarding our modelling approach. In order to propose a plausible ICER range for the Committee's consideration we revisit the following technical aspects regarding the OS modelling approach.	Comments noted
Lilly UK – ACD2	**Choice of parametric distribution for projective OS modelling**: Lilly believes that the ERG's alternative model using exponential projective modelling is biased against pemetrexed and as a result consider it to be a less appropriate model than Lilly's model that uses a gamma distribution. Lilly consider the gamma distribution to be the best fit to the observed OS data from the PARAMOUNT trial and have provided full details of the curve-fitting exercise and a wide range of evidence in support of our modelling approach. In addition, the Committee has inappropriately attributed the post-progression survival (PPS) gain in the model to the use of the gamma distribution (paragraph 4.15 of the FAD/second ACD), when in fact, the key driver of PPS gain in the model is the assumption of continued treatment effect on OS in the post-trial period. We believe this misunderstanding has been a major concern for the Committee and has been the main factor leading to their rejection of Lilly's modelling approach. We address this concern.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	**Selection of cut point for projective OS modelling**: Lilly have serious concerns regarding the ERG's selection of a cut point with a common survival level of 37.2% in both arms to begin survival projection in their exponential model, since it results in a considerable underestimation of OS benefit in the pemetrexed arm. The ERG did not present any evidence or compelling rationale for their alternative strategy and we are concerned that this approach has not been acknowledged or adequately scrutinised by the Committee. In contrast, we presented (in our response to the second ACD) a clear rationale for our preferred cut point of 25%, implemented in a gamma model, which avoids this underestimation by using more of the observed trial data.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	**Calculation of the size of the pemetrexed-eligible patient population for consideration of pemetrexed continuation maintenance under the 'End of Life' supplementary advice:** We consider that double-counting of patients eligible for pemetrexed switch maintenance is inappropriate and unfair, since these patients can, by definition, only receive pemetrexed once in the entire treatment pathway and do not represent an additional population of patients who may receive such therapy. Furthermore, the number of PS 2 patients eligible to receive pemetrexed in the second-line setting has been substantially overestimated.	The Committee noted comments received during consultation on the second ACD regarding the counting of patients eligible for 'switch maintenance'. These patient numbers are no longer counted. See section 4.23 of the third ACD. Comment noted
Lilly UK – ACD2	**Ethical considerations around withdrawal of pemetrexed continuation maintenance treatment:** We believe that withholding pemetrexed treatment from patients in whom pemetrexed/cisplatin first-line has already proved beneficial is unfair and likely to be perceived as unethical by patients and physicians in clinical practice.	Comments noted. Potential issues relating to equality legislation are discussed in section 4.28 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	**Summary of overall survival modelling approach and plausible ICER range** In summary, Lilly believes that our survival modelling approach, based upon systematic curve-fitting using best practice NICE Technical Support Document (TSD) guidance (Latimer, 2011), is fundamentally sound and robust, since it is supported by a wide range of evidence that strongly suggests that we have chosen the most appropriate parametric distribution to project OS. We believe the Committee did not adequately consider all of the evidence supporting the choice of the gamma distribution. In addition, we address the Committee's concern regarding the PPS gain in our basecase analysis, and demonstrate that the key driver of PPS gain in the model is the assumption of continued treatment effect on OS in the post-trial period, i.e. whether the treatment benefit on OS continues beyond the observed trial period or stops immediately at the end of the trial, rather than the use of the gamma model. In contrast, the ERG has presented a single alternative modelling approach based upon visual assessment of the survival curves, which we are concerned provides a poor fit to the pemetrexed OS data and consequently is biased against pemetrexed. The ERG has not provided adequate justification by presenting any sensitivity analyses exploring alternative parametric models together with standard statistical tests used to compare the goodness of fit of alternative models, both of which are important elements when considering uncertainty associated with the analysis of survival data (Latimer, 2011). We believe it is essential that the ERG's modelling approach is subjected to the same level of scrutiny as that applied to our model, with the same range of curve-fitting, statistical tests and validation to enable a fair and reasonable comparison between the two approaches. In the absence of such testing the Committee is substantially prejudiced in its ability to make a direct comparison of the goodness of fit of the two approaches and we believe is simply not in a position to make an informed decision about the validity of the ERG's methodology and whether their approach or that presented by Lilly should be preferred. We have already explained why our modelling approach is robust, and having addressed the Committee's concerns regarding the PPS gains seen in the basecase analysis, have demonstrated that the plausible ICER range is likely to fall within the range £59,000 to £69,000, most likely in the mid range, i.e. £60,000 - £65,000 if the Committee accepts that a clinically-plausible post-trial OS treatment effect falls somewhere between the two alternative scenarios included in the model.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	**Choice of parametric distribution for projective OS modelling** Lilly believes that the ERG's alternative model using exponential projective modelling is biased against pemetrexed and, as a result, consider it to be a less appropriate model than Lilly's model which uses a gamma distribution.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	The ERG presented an alternative OS model based on independent exponential projective OS modelling for each arm. The rationale given for this modelling approach was that exponential trend lines fitted to the cumulative hazard plot (Fig 10, ERG Report, December 2012) run in parallel, after the first year. The ERG states that this finding indicates a similar long-term mortality risk in each arm, i.e. the OS hazard rate is constant over time.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	The ERG's cumulative hazard plot, reproduced below (Figure 1), shows that the fitted hazard line provides a reasonable visual fit to the observed pemetrexed OS data initially, i.e. between days 200 to 600 approximately. However, the highlighted section of the pemetrexed arm shows the fitted hazard line is consistently higher than the actual trial data for a considerable proportion of the trial period from around day 600 until the end of the trial (day 1050 approx.). This indicates that the fitted hazard line is overestimating the hazard in the pemetrexed arm and that the actual observed hazard in the pemetrexed arm is not constant after the first year. It appears to be slightly lower in the latter part of the observed data (days 600 to 1050 approx.) compared to earlier (days 200 to 600 approx.).	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	The ERG also states that their fitted exponential models show close correspondence to the observed OS data (Fig 11, ERG Report, December 2012). Figure 2 below reproduces the ERG's fitted exponential model plot. This shows that the ERG's OS model does not fit the pemetrexed data well, consistently underestimating the observed OS data from around day 600 until the end of the trial. Since the ERG's model underestimates the observed OS data in the tail of the pemetrexed arm, it will therefore also bias the entire projective modelling for the pemetrexed arm in the post-trial period.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	The ERG's use of the exponential distribution assumes that the hazard rate is constant over time. This is not supported by the OS data from the PARAMOUNT trial. The plots of the smoothed hazard estimates for PARAMOUNT OS data (Figures 3 and 4 overleaf) show that in both treatment groups the hazard initially increases and then decreases over time i.e. it is <u>not</u> constant. An exponential model therefore fails to capture the initial increase and subsequent decrease in the baseline hazard evident in the observed PARAMOUNT data. The ERG appear not to have investigated whether alternative distributions that allow the hazard to change over time, e.g. the gamma distribution, provided a better fit to the observed data as they did not present any alternative parametric forms in sensitivity analyses or any goodness-of-fit statistics.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	An exponential function, as recommended by the ERG is depicted by the two horizontal lines in Figure 3 above and assumes that the hazard rate is constant over time. In contrast, the gamma model (Figure 4 above) predicts the underlying hazard to initially increase and then decrease, and therefore better reflects PARAMOUNT OS data, and thus appears to offer a better fit to the observed PARAMOUNT OS data. In addition to the issues raised above regarding the poor fit of the ERG's exponential model to the observed pemetrexed OS data, Lilly are also concerned about the selection of the starting points for the ERG's projective OS models. Whilst this issue is related to the cut-point issue discussed later in the document, we discuss it below in the context of the ERG's exponential model since we believe that it introduces an additional source of bias.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

<table>
<tr><th>Consultee / Document</th><th>Comment</th><th>Response</th></tr>
<tr><td>Lilly UK – ACD2</td><td>The ERG used visual inspection of the cumulative hazard plot to determine where to start their OS models; fitting their OS projective model from cycle 19 in the placebo arm and cycle 8 in the pemetrexed arm (Details of amendments, LRiG, October 2012). The ERG provided no other rationale for this choice, and subsequent examination of the survival data in the economic model (Lilly model: Lifetable worksheet) shows that the ERG's OS model for the pemetrexed arm was fitted to a point where patient characteristics for both progression-free survival (PFS) and OS are very substantially different to those in the placebo arm, which is likely to introduce a further source of bias. Table 1 overleaf shows that only 5% of patients remain progression-free at cycle 19 in the placebo arm compared with 46% of patients at cycle 8 in the pemetrexed arm. In addition the % survival is very substantially different in the two arms: 42% for placebo and 81% for pemetrexed (Table 1). The ERG does not discuss this important issue and no clear rationale is provided for their original approach. This is surprising, when in their first report they stated the importance of a common survival rate to determine the point at which projection takes over from the KM data (LRiG, Dec 2012). In addition, no sensitivity analyses were presented by the ERG in terms of implementing alternative starting points for their projective modelling.

Table1. Patient characteristics at the starting point of the ERG's projective OS models. (Lifetable worksheet, Lilly model)
<table>
<tr><th colspan="3">Survival data</th></tr>
<tr><th></th><th>Placebo – cycle 19</th><th>Pemetrexed – cycle 8</th></tr>
<tr><td>PFS
% of cohort at risk of progression</td><td>5%
n=9</td><td>46%
n=165</td></tr>
<tr><td>OS
% of cohort at risk of death</td><td>41%
n=74</td><td>83%
n=298</td></tr>
<tr><td>OS
% survival</td><td>42%</td><td>81%</td></tr>
</table></td><td>The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data.

See section 4.16 of the third ACD.</td></tr>
</table>

Consultee / Document	Comment	Response
Lilly UK – ACD2	**Lilly's modelling approach** Lilly consider the gamma distribution to be the best fit to the observed KM data from the PARAMOUNT trial having provided full details of the curve-fitting exercise in our original submission and a wide range of evidence in support of this choice in response to the first ACD stage. We believe the Committee did not adequately consider all of the evidence supporting the choice of the gamma distribution. In addition, we address the Committee's concern regarding the PPS gain that occurs in our basecase analysis, which the Committee inappropriately attributed to the use of the gamma model. We demonstrate that it is, in fact, the assumption concerning post-trial treatment effect on OS that is the key driver of PPS gain in our model. As such, we do not believe the Committee should reject the gamma distribution in favour of the ERG's exponential OS model.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	The ERG did not comment on this evidence in their Addendum (LRiG, April 2013), nor was it discussed at the second Committee meeting beyond initial presentation of comments received during the first ACD consultation. As a result, we believe the Committee did not give adequate consideration of the evidence supporting the choice of the gamma distribution. For convenience, this evidence is reproduced in Appendix 1.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	The Committee was concerned about the proportion of survival that occurred post-progression in our basecase analysis and has inappropriately attributed the post-progression survival (PPS) gain to the use of the gamma distribution. In fact, the key driver of PPS gain is the assumption of continued treatment effect on OS in the post-trial period.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	Lilly explored two alternative assumptions concerning post-trial treatment effect on OS in the model. These assumptions predict the shape of the extrapolated survival OS curves in the post-trial period, i.e. beyond the observed trial duration, and should take account of the clinical plausibility of each assumption. A continuous benefit assumption was chosen for our basecase analysis, based on clinical expert opinion during model development. This assumes that the statistically significant OS hazard ratio (HR) observed during the trial period (HR=0.78, p= 0.034) continues in the extrapolation period. An alternative 'one-time benefit' assumption was included in the model. This assumes that the OS benefit (HR=0.78), observed in the pemetrexed arm during the trial, ends immediately upon cessation of the trial, i.e. the HR reverts to 1.0 at the end of the observed trial period. Given that the trial endpoint is effectively an arbitrary time point, when sufficient deaths have been observed for a robust assessment of benefits versus risks to be conducted for regulatory purposes, this latter scenario was not considered to be clinically plausible but was included in the model, to represent a conservative scenario in our sensitivity analyses. Whilst the Committee accepted this latter scenario may not be clinically plausible, they seem to have interpreted this assumption as affecting the OS treatment effect after treatment has been discontinued, i.e. after disease progression, rather than after the entire trial period, and have attributed the PPS gain seen in the basecase analysis solely to the use of the gamma distribution (paragraph 4.15, ACD, August 2013). Since this assumption affects the shape of the OS curve beyond the trial duration it directly influences the total OS estimated when the model is extrapolated over a lifetime horizon. The PFS data may be considered effectively fully mature (p55, ERG report, December 2012) and does not require extrapolation. When OS is extrapolated to a lifetime horizon additional OS gains will be accrued above and beyond those seen in the trial. Since PPS is a function of OS and PFS, i.e. PPS=OS-PFS, when the alternative assumptions for post-trial treatment effect on OS are implemented the PPS benefit will increase or decrease in line with the OS gains as shown in Table 2	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

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<tr><th>Consultee / Document</th><th>Comment</th><th>Response</th></tr>
<tr><td>Lilly UK – ACD2</td><td>

Table 2. Modelled incremental mean survival (Lifetime analysis from randomisation to maintenance treatment; discounted results)

<table>
<tr><th>Assumption modelled</th><th colspan="2">Incremental survival Months</th><th>Incremental survival % of OS</th><th>ICER £/QALY gained</th></tr>
<tr><td rowspan="3">Gamma distribution with continuous benefit assumption

i.e. basecase scenario</td><td>PFS</td><td>3.24</td><td>79 %</td><td rowspan="3">Revised basecase after first ACD:

£58,918</td></tr>
<tr><td>PPS</td><td>0.84</td><td>21 %</td></tr>
<tr><td>OS</td><td>4.08</td><td></td></tr>
<tr><td rowspan="3">Gamma distribution with one-time benefit assumption

i.e. conservative scenario</td><td>PFS</td><td>3.24</td><td>93 %</td><td rowspan="3">Sensitivity analysis:

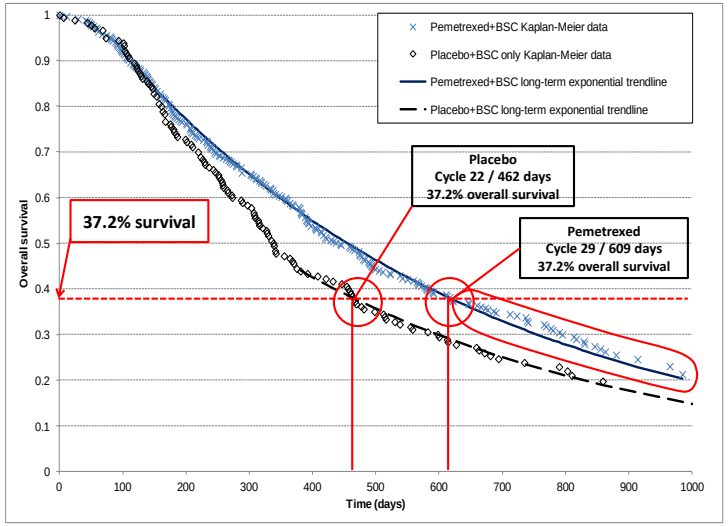
£68,771</td></tr>
<tr><td>PPS</td><td>0.24</td><td>7 %</td></tr>
<tr><td>OS</td><td>3.48</td><td></td></tr>
</table>

Note: numbers may not sum exactly due to rounding

</td><td>Table and data noted.</td></tr>
<tr><td>Lilly UK – ACD2</td><td>The results in Table 2 show that in the revised basecase analysis presented in our response to the first ACD, with a continued OS benefit assumption implemented, 21% of the incremental OS benefit is estimated to occur in the post-progression period. This analysis led to an ICER of £58,918. However, when the alternative ‘one-time benefit’ assumption is implemented only 7% of the incremental OS benefit occurs in the post-progression period and the resulting ICER is £68,771. These results clearly demonstrate that it is this assumption, and not the use of the gamma distribution per se, that results in the majority of the PPS gain seen in our basecase analysis.</td><td>The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data.

See section 4.16 of the third ACD.</td></tr>
</table>

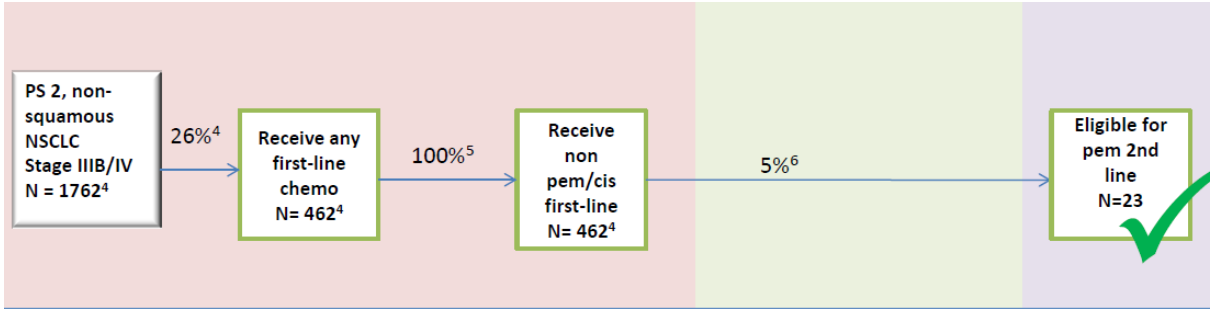
Consultee / Document	Comment	Response
Lilly UK – ACD2	By definition, no-one knows what happens to the HR for OS after the end of the trial since data is no longer collected. What we do know however, is that the PARAMOUNT trial was powered for OS benefit. With a median follow up of 24 months for alive patients the data provides robust insight about the OS benefit over the entire observed period. We believe the true value for the OS HR in the post-trial period is likely to fall somewhere between the two assumptions modelled, i.e. a HR between 0.78 and 1.0, and therefore propose a plausible ICER range within the range £59,000 to £69,000, most likely in the mid range, i.e. £60,000 - £65,000, if the Committee accepts that a clinically-plausible post-trial OS treatment effect falls somewhere between the two alternative scenarios included in the model, based on the Lilly gamma model with a 25% survival cut point.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	**Selection of cut point for projective OS modelling** Lilly have serious concerns regarding the ERG's preferred approach of selecting a cut point with a common survival level of 37.2% in both arms, and believe it to be highly biased against pemetrexed. We believe the Lilly cut point of 25% survival implemented in the gamma model is more appropriate.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	The evolution of the choice of cut point from Lilly's original submission to the Committee's final preference in the second Appraisal Consultation Document (ACD) is somewhat complex. As such, we provide a summary of the procedural history relevant to this point in Table 1 (Appendix 2) together with a summary of survival characteristics for each proposed cut point (Table 2, Appendix 2).	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	The ERG's rationale for selecting a 37.2% cut point was that their OS projection model, as presented in the first ERG report (LRiG, December 2012), corresponded precisely with the KM estimates at this point, and as a result, claimed that this was an "improved bias-limiting method" (ERG Addendum, LRiG, April 2013). However, the ERG did not provide any explanation for why they considered this was more appropriate than their original modelling approach, which had employed projective starting-points much earlier on in the survival curves (from cycle 8 in the pemetrexed arm and from cycle 19 in the placebo arm) rather than use cut points in the tail of the survival curves, the approach used in Lilly's model. The ERG's projective OS models, now implemented using a 37.2% cut point, rather than the original starting points, remains subject to the imbalance in PFS and OS status of patients in each arm as highlighted earlier (See Section 1a above and Table 2, Appendix 2).	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	**Figure 5. Comparison of OS in both arms of the PARAMOUNT trial with ERG calibrated exponential long-term models with the 37.2% survival cut points** (Reproduced from Fig 10, ERG Report, LRiG, December 2012: annotations added by Lilly)  	Figure noted.

Consultee / Document	Comment	Response
Lilly UK – ACD2	If Figure 11 from the ERG's original report is re-examined (Figure 5 above), it can be clearly seen that using a common survival level of 37.2% under-estimates every single point of the observed OS data for the projective period of the pemetrexed arm, whilst providing a good fit to the placebo arm, thus clearly introducing a substantial bias against the pemetrexed arm. This underestimation of observed OS benefit in the pemetrexed arm raises substantial concerns in relation to the choice of cut point – but has not been taken into account or even acknowledged by the ERG or the Committee.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	While the most appropriate choice of cut point between the observed data and the modelled extrapolation is acknowledged by all parties to be a matter of judgement, that judgement should be exercised fairly and reasons given for the point selected. The best practice NICE TSD states: "Both the Gelber method and the LRiG Exponential method are likely to be sensitive to the point at which the parametric model takes over from the Kaplan Meier and therefore if either of these methods are used it is important to provide clear rationale for the switch point using statistical analysis." (page 35, Latimer, 2011)	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.
Lilly UK – ACD2	There was no discussion during the second Committee meeting seeking to investigate whether the ERG's proposed new approach did in fact reduce or eliminate all potential sources of bias, or indeed if it introduced additional sources of bias. As a result, in contrast to the scrutiny given to Lilly's approach, the ERG's preferred cut-point approach was not subjected to adequate or any real scrutiny. Furthermore the conclusion expressed in the ACD (para 4.16, Aug 2013) is simply that the "Committee was aware that the choice of cut point is a matter of judgement and, as such, any estimates come with some degree of uncertainty" and that, "acknowledging this uncertainty, the Committee accepted the ERG's basis for the choice of 37.2% as the point from which to begin survival projection". Considering that this approach represented a significant change from the ERG's original modelling approach and also discarded both the 20% survival cut point recommended by the ERG and preferred by the Committee (para 4.15, ACD, February 2013) and the 25% survival cut point proposed by Lilly, the Committee should have provided specific reasons for accepting this change.	The Committee concluded that extrapolation of the data was not needed and that their decision on cost-effectiveness should be made on the basis of actual data. See section 4.16 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	Lilly's original, and consistent, stated rationale for an appropriate cut-point approach is one that uses as much of the observed KM data as possible, whilst still having a sufficient number of patients informing the survival curves at that point to provide a reliable estimate of survival at and beyond the point where the extrapolation joins the observed data. Having initially employed a cut point based on a % 'at risk of death' in our original basecase analysis, following the first ACD Lilly accepted the ERG's preferred cut point approach using % survival applied to the gamma model. However, whilst the ERG had recommended a 20% survival cut point, based on only 19 patients in the placebo arm and 16 patients in the pemetrexed arm, Lilly considered a 25% survival cut point to be more appropriate since this cut point is informed by data from 42 patients in the placebo arm and 44 patients in the pemetrexed arm. As such, Lilly considered the 25% survival cut point to be consistent with our previously stated rationale providing a more robust extrapolation compared to the 20% survival cut point. As stated above, a summary of survival characteristics for each proposed cut point is presented in Table 2, Appendix 2	Comments noted.
Lilly UK – ACD2	**Calculation of the size of the pemetrexed-eligible patient population for consideration of pemetrexed continuation maintenance under the 'End of Life' supplementary advice** The approach followed by the Committee in determining the population size is unfair and does not reflect the current use of pemetrexed in clinical practice. As stated in our response to the first ACD, while we accept the Committee's estimates of eligible population size for first-line non-squamous NSCLC (n=4,555), malignant pleural mesothelioma (n=1,606) and continuation maintenance (N=588) populations, we believe that the double-counting of patients eligible to receive pemetrexed switch maintenance treatment is completely inappropriate. Also, the Committee's estimate for Performance Status (PS) 2 patients at first-line who are then only eligible for pemetrexed at second-line is excessively high (n=462, ACD paragraph 4.24). A figure showing Lilly calculations of patients eligible for pemetrexed across all indications which was provided with our response to the first ACD is reproduced in Appendix 3 for ease of reference.	Comments noted. The estimated size of the population eligible to receive pemetrexed maintenance treatment has been revised within the third ACD to reflect consultation comments. See section 4.23

Consultee / Document	Comment	Response
Lilly UK – ACD2	**Double-counting of switch maintenance patients** The 1,500 patients estimated to be switch maintenance eligible in paragraph 4.23 of the ACD are essentially a sub-group of the 4,555 patients with PS 0-1, non-squamous histology and advanced disease who represent the maximum population of PS 0-1 NSCLC patients who can ever be eligible for pemetrexed therapy - irrespective of the particular regime or place in the treatment pathway. These 1,500 patients eligible for pemetrexed switch maintenance have been accounted for already in the group of 4,555 pemetrexed-eligible patients and cannot, by definition, receive pemetrexed under both indications. These patients should not be counted twice since they will only receive pemetrexed in one setting, either first-line or switch maintenance, but certainly not both. Switch maintenance by definition excludes patients who received pemetrexed/cisplatin first-line. Double-counting of these patients does not reflect the licensed indication for pemetrexed or the way pemetrexed is used in actual clinical practice and is therefore totally unjustified and unfair, because it artificially increases the number of pemetrexed-eligible patients. NICE's supplementary advice on appraising life extending, end of life treatments, issued in July 2009, provides some explanation for the small patient population criterion at paragraph 1.3, which states *"In addition, the Institute has taken account of its responsibility to recognise the potential for long term benefits to the NHS of Innovation. In this context, it considers it appropriate for its Appraisal Committees to have regard to the importance of supporting the development of innovative treatments that are anticipated to be licensed for small groups of patients who have an incurable illness".*	Comments noted. The estimated size of the population eligible to receive pemetrexed maintenance treatment has been revised within the third ACD to reflect consultation comments. See section 4.23
Lilly UK – ACD2	The approach of the Appraisal Committee in relation to assessment of the small patient population for pemetrexed is inconsistent with the rationale given in the supplementary advice. First-line chemotherapy, switch maintenance and continuation maintenance treatment are separate indications each requiring its own clinical development programme. Receipt of first line treatment with pemetrexed precludes eligibility for switch maintenance (in the same way as other patient characteristics such as poor performance status would preclude eligibility.) By double counting first line and switch maintenance the Appraisal Committee is undermining *"the development of innovative treatments" "licensed for small groups of patients who have an incurable illness"* rather than supporting such development. Accordingly Lilly believes such double counting is inappropriate, unreasonable and unfair.	Comments noted.

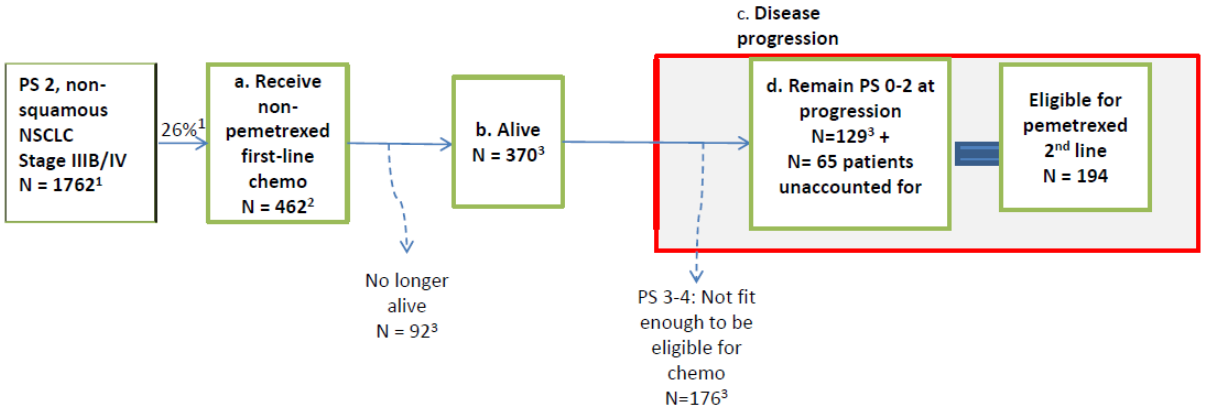
Consultee / Document	Comment	Response
Lilly UK – ACD2	**PS 2 patients eligible for pemetrexed monotherapy in the second-line setting** As stated in our response to the first ACD, we consider that as per the available evidence and clinical opinion, the number of PS 2 patients eligible to receive pemetrexed second-line treatment is much lower than the figure of 462 mentioned in the ACD, at approximately 23. We reproduce an extract from the figure presented as part of our response to the first ACD in order to illustrate how this figure has been derived: **Figure 6. Lilly calculations of PS 2 patients eligible for pemetrexed second-line**  Data from the National Lung Cancer Audit (NLCA) 2011 cohort shows that there are 1,762 patients with non-squamous stage IIIB/IV NSCLC with PS 2 (Personal communication, Dr M. Peake, 2013). Of the 1,762 PS 2 patients identified in the 2011 NLCA, 462 received first-line chemotherapy. Since only 5% of patients receiving first-line chemotherapy are estimated to be eligible for second-line treatment (Personal communication, Dr J. Lester, March 2013), only 23 patients are estimated to be eligible for second-line treatment, based on clinical expert opinion.	Comments noted.

Consultee / Document	Comment	Response
Lilly UK – ACD2	In calculating the number of PS 2 patients eligible for pemetrexed second-line treatment, the Committee have not taken into consideration the factors that preclude patients from receiving second-line chemotherapy in actual clinical practice. Patients with PS 2 are not considered fit enough to receive platinum-based chemotherapy (i.e., cisplatin or carboplatin doublets) in the first-line NSCLC setting and therefore receive non-pemetrexed treatment regimens. Only a fraction, i.e. 5%, of these patients would survive first-line treatment with adequate performance status to ultimately become candidates for pemetrexed monotherapy second-line. In the pivotal second-line NSCLC trial, JMEI (Hanna et al 2004), the majority of patients were of PS 0 -1, with only a small proportion of PS 2 patients (11.4% and 12.4% respectively in the pemetrexed and docetaxel arms). The Committee have assumed that ***all*** patients who receive non-pemetrexed first-line treatment would be eligible for pemetrexed monotherapy second-line. This is an overestimate unsupported by currently available evidence. The latest quarterly data (April – June 2013) from the National Cancer Drugs Fund (NCDF), shows a mere 10 patients have actually received pemetrexed second-line treatment between April-June 2013. While these numbers refer to actual usage rather than eligible population, they serve to highlight how unrealistic the Committee's estimate is, and that in all likelihood, eligible patient numbers are unlikely to exceed double figures. We request the Committee to keep these low figures in mind during their deliberations.	Comments noted.
Lilly UK – ACD2	We maintain that the eligible patient population for pemetrexed across all indications is less than 7,000, i.e., 4,555 first line NSCLC + 588 continuation maintenance + 0 switch maintenance (since these patients already counted as part of the 4,555 first-line patients, first-line and switch maintenance being mutually exclusive indications) + 23 PS 2 patients second-line + 1,606 mesothelioma = **6,772 pemetrexed eligible patients**. Pemetrexed continuation maintenance should therefore be considered under the 'End of Life' supplementary criteria.	Comments noted.
Lilly UK – ACD2	**Ethical considerations around withdrawal of pemetrexed continuation maintenance treatment** In the light of the realistic estimates of patient numbers eligible for pemetrexed (i.e., 6772 patients), Lilly respectfully requests the Committee to carefully consider the impact of their final decision on patients. As stated previously, the negative recommendation for pemetrexed continuation maintenance will have the unfair and clinically unacceptable consequence of pemetrexed treatment being withdrawn from the small group of patients who are currently eligible to receive pemetrexed continuation maintenance (N=588, likely to be lower as shown by quarterly figures from the NCDF), having experienced complete/partial response or stable disease on pemetrexed/cisplatin first-line therapy.	Comments noted. Potential issues relating to equality legislation are discussed in section 4.28 of the third ACD.

Consultee / Document	Comment	Response
Lilly UK – ACD2	The Committee's recommendation puts clinicians in the difficult position of having to explain and justify withdrawal of effective treatment from patients who have shown clear benefit from pemetrexed/cisplatin first-line, while simultaneously being able to offer pemetrexed maintenance treatment to patients receiving non-pemetrexed first-line regimens. This differential advice, based upon the first-line treatment option, is likely to be complex and challenging for clinicians to implement in clinical practice and potentially inequitable. The withdrawal of pemetrexed treatment from this small group of patients who could potentially continue to experience improved survival as a result of pemetrexed continuation maintenance treatment is likely to be perceived as confusing, unfair and counterintuitive by patients and create ethical dilemmas for clinicians.	Comments noted. Potential issues relating to equality legislation are discussed in section 4.28 of the third ACD.
Lilly UK – ACD2	Paragraph 4.28 of the second ACD considers whether the refusal to recommend continuation maintenance treatment constitutes a breach of equality legislation. The Committee concludes that first-line treatment with pemetrexed is not a protected characteristic and states that '*even if there was any unfairness, given the high ICER of approximately £82,000 per QALY gained, the Committee agreed that the recommendation could be justified…..*'. For completeness, as indicated previously, the ICER of £82,000 was based on the ERG's changes to Lilly's economic model, which Lilly strongly believes are inappropriate; nor were they adequately explored or scrutinised by the NICE technical team or the Committee and are currently also the subject of this consultation. As a result, we do not believe that the recommendation can be justified, as stated in the ACD.	Comments noted.
Lilly UK – ACD2	The outlook for patients with NSCLC is poor with median overall survival being approximately 6 months (NLCA information sheet 2011). Pemetrexed continuation maintenance could potentially improve survival in this group of patients who have limited treatment options. We hope that the Committee will take into consideration the data presented in our response during their deliberations and will arrive at a decision that is in the interest of this small group of patients who expect to receive pemetrexed monotherapy in the continuation maintenance setting after having experienced the benefits of pemetrexed/cisplatin first-line.	Comments noted.

Consultee / Document	Comment	Response
Lilly UK – ACD3	We welcome the acknowledgement in the ACD that there had been double-counting of the switch-maintenance patients in calculating the size of the patient population eligible for pemetrexed. However, we believe that the current approach to calculating the size of the PS 2 patient population eligible for pemetrexed second-line treatment overestimates the population size.	Comments noted.
Lilly UK – ACD3	*PS 2 patients eligible for pemetrexed monotherapy in the second-line setting* To accurately estimate the size of the patient population eligible for pemetrexed second-line treatment, we need to define eligibility criteria for second-line treatment in general. Second-line treatment is defined as any treatment administered to patients who have experienced disease progression after first-line treatment. To become eligible for pemetrexed second-line treatment, patients need to fulfil the following requirements: 1. Receive non-pemetrexed first-line treatment 2. Remain alive through first-line treatment cycles and the period between cessation of first-line treatment and disease progression or relapse (some patients die during this time, before becoming eligible for second-line treatment) 3. Experience disease progression after first-line treatment 4. Remain of adequate performance status (PS 2 or better) after disease progression so as to remain fit enough to be eligible for chemotherapy	Comments noted.

Consultee / Document	Comment	Response
Lilly UK – ACD3	**Estimation of patient numbers** Data from the NLCA 2011 cohort shows that there are a total of 1,762 patients with non-squamous stage IIIB/IV NSCLC with PS 2 (Personal communication, Dr M. Peake, 2013), of which, 462 received any first-line treatment. We assumed that all 462 of these patients received non-pemetrexed first-line treatment based on their performance status. According to the eligibility criteria a) above, this is our starting population to calculate the number of patients eligible for pemetrexed second-line treatment. In the absence of national audit data on the fate of these patients, we conducted a clinician survey to determine the number of PS 2 patients eligible for second-line treatment. Estimates of patient numbers were calculated based on the responses of five clinicians who completed the survey and consented to their details being reported in our response (see Appendix 1). Results showed that of the 462 patients who receive first-line treatment, 20% (N=92) of patients actually die before disease progression (i.e. before becoming candidates for second-line therapy); a further 38% (N=176) deteriorate to PS 3-4 and become ineligible for pemetrexed second-line treatment; 28% (N=129) are of PS 0-2 and remain eligible for pemetrexed second-line treatment. This leaves about 14% (N=65) patients unaccounted for. Adding this number to the population of patients eligible for pemetrexed to ensure all patients are accounted for yields a maximum plausible estimate of 42% of patients (i.e. N=129 + 65 =194) eligible for pemetrexed second-line treatment.	Comments and revised estimate of the population patients eligible for pemetrexed second-line treatment noted. The estimated population eligible for second-line treatment with pemetrexed has been revised within the FAD. See section 4.24
Lilly UK – ACD3	To summarise, the total number of patients eligible for pemetrexed treatment for all licensed indications, as accepted by the Appraisal Committee and mentioned in the 3rd ACD is as follows: • PS 0-1 non-squamous NSCLC patients eligible for pemetrexed first-line: N = 4,555 • Patients eligible for continuation maintenance treatment with pemetrexed: N=588 • Patients eligible for switch maintenance treatment with pemetrexed: N=0 (already counted in the first-line population of N=4,555) • Patients with malignant pleural mesothelioma (MPM) eligible for pemetrexed: N= 1,606 • PS 2 patients eligible for pemetrexed second-line treatment: N = 194	Comments noted. The estimated total population eligible for pemetrexed has been revised with the FAD. See section 4.26
Lilly UK – ACD3	• We would like to point out that the methodology used to arrive at the number of PS 2 patients eligible for pemetrexed second-line treatment is similar to that used in estimating eligible patient numbers for other indications of pemetrexed in this appraisal which have already been accepted by NICE (see Lilly responses to 1st and 2nd ACD).	Comment noted.

Consultee / Document	Comment	Response
Lilly UK – ACD3	Data from the National Cancer Drugs Fund (NCDF), shows that only 14 patients received pemetrexed second-line treatment between April – September 2013. Although these numbers refer to actual usage rather than eligible population, they suggest that the eligible patient population is considerably smaller than 462. Our estimates, based on the clinician survey establish that the number of patients eligible for second-line treatment according to the third ACD (N=462) is an overestimate and that the maximum eligible patient number is 194. **Figure 1. Estimation of PS 2 patients eligible for pemetrexed second-line treatment based on clinician survey according to the eligibility criteria defined above**  [1] Personal communication, Dr M. Peake: data extraction from National Lung Cancer Audit Database (2011 cohort); Data from the National Lung Cancer Audit (NLCA) 2011 cohort shows that there are 1,762 patients with non-squamous stage IIIB/IV NSCLC with PS 2 (Personal communication, Dr M. Peake, 2013).; [2] Assumption based on the fact that only patients with PS 0-1 would be eligible for pemetrexed first-line treatment; [3] Average values from responses to clinician survey (see Appendix 5).	Comments and population estimates noted. The estimated population eligible for second-line treatment with pemetrexed has been revised within the FAD. See section 4.24
Lilly UK – ACD3	We therefore maintain that the maximum plausible estimate for the eligible patient population for pemetrexed across all licensed indications is less than 7,000, at **6,943 patients** (i.e., 4,555 PS 0-1 first-line NSCLC + 588 continuation maintenance + 0 switch maintenance + 194 PS 2 patients second-line + 1,606 mesothelioma).	Comments noted.

Consultee / Document	Comment	Response
Lilly UK – ACD3	Also the estimated 4,555 patients eligible for first-line treatment includes 10%-15% (N= 456 to N= 683) of patients who are EGFR mutation positive (Final scope, Afatinib EGFR positive locally advanced or metastatic NSCLC. ID556; Costing statement for TA258). Although in theory, these patients are eligible to receive pemetrexed and therefore are included in the calculation above, in clinical practice, EGFR positive patients would receive erlotinib or gefitinib rather than pemetrexed. This is corroborated by the fact that in the NICE afatinib appraisal pemetrexed was not considered as a comparator based on clinical expert feedback that pemetrexed would rarely be used in the EGFR positive population. If the Appraisal Committee were to agree that these patients, though in theory eligible, would not get pemetrexed in clinical practice, this would further reduce the total maximum plausible estimated population by 10% (456 patients) to **6,487** patients. This has not been taken into consideration so far in the calculation of eligible patient numbers for pemetrexed but highlights the fact that the figure of 7,200 in the third ACD is an overestimate and that pemetrexed continuation maintenance should be considered under the 'End of Life' supplementary criteria.	Comments noted.
Lilly UK – ACD3	**Cost-effectiveness** We acknowledge the ERG's new approach, which proposes a simple graphical method to re-estimate the mean overall survival (OS) benefit for pemetrexed versus placebo. Their revised estimate of 3.49 months falls at the low end of Lilly's estimated plausible range of 3.48 - 4.08 months submitted in response to the second ACD (Table 2, Lilly response to ACD2, date). We are pleased to see that although Lilly and the ERG have used different approaches during this appraisal the final estimates of OS gain and associated ICERs are very similar. We have included in Appendix 2 some technical considerations that we believe might be of interest to the ERG and the Appraisal Committee.	Comments noted.
Lilly UK – ACD3	**Conclusion** We hope our response has demonstrated that that the maximum plausible estimate for the eligible patient population for pemetrexed across all licensed indications is less than 7,000, at 6,943 patients. We accept that the most plausible ICER remains above the implied threshold used in previous appraisals considered under the End of Life Supplementary advice. In view of the small patient population that pemetrexed continuation maintenance is indicated for (N=588), the additional survival benefit for patients who have already received pemetrexed in the first line treatment setting, and the fact that pemetrexed offers a new treatment paradigm for patients with a poor prognosis, we hope the Appraisal Committee will reconsider their decision regarding End of Life and use of this treatment in clinical practice.	Comments noted. The estimated size of the total population size for which pemetrexed has a licence has been updated. See section 4.26 of the FAD.

Consultee / Document	Comment	Response
Lilly UK – Additional evidence (10.01.14)	Thank you for the opportunity to review and respond to the updated estimates of the eligible patient population for pemetrexed in advance of the fourth Appraisal Committee meeting. We have reviewed the updated estimates based on the latest 2012 NLCA data and accept the patient numbers for first-line NSCLC (N=4,898) provided in your letter. We have also updated the numbers for continuation maintenance in accordance with the latest 2012 NLCA data for consistency. This increases the patient population from N=632 to N=654, since the audit data show that 57.2% of PS 0-1 non-squamous NSCLC patients received chemotherapy. As stated in our response to the third ACD (submitted 18th December), we believe the estimated number of patients with performance status (PS) 2 eligible for second-line treatment with pemetrexed should be N=194. We sought updated estimates for pemetrexed in malignant pleural mesothelioma (MPM), to ensure consistency with the updated NSCLC estimates. The latest data from the NLCA 2012 (personal communication, Dr. Beckett on behalf of NLCA project team, 9th January 2014) show that 61.1% of mesothelioma patients with advanced disease are eligible for chemotherapy. As a result, the total population of patients with advanced mesothelioma and PS 0-1 eligible to receive pemetrexed in combination with cisplatin is N=1,056 (see enclosed Table 1 for calculations). To summarise, the total number of patients eligible for pemetrexed treatment for all indications is as follows: • PS 0-1 non-squamous NSCLC patients eligible for pemetrexed first-line: N=4,898 • Patients eligible for continuation maintenance treatment with pemetrexed: N=654 • PS 2 patients eligible for pemetrexed second-line treatment: N=194 • PS 0-1 advanced malignant pleural mesothelioma (MPM) patients eligible for pemetrexed: N=1,056	Comments noted. The estimated size of the total population size for which pemetrexed has a licence has been updated. See section 4.26 of the FAD.

Consultee / Document	Comment	Response
Lilly UK – Additional evidence (10.01.14)	We believe that the updated maximum plausible estimate for the eligible patient population for pemetrexed across all licensed indications is **6,803 patients** (i.e., 4,898 PS 0-1 first-line NSCLC + 654 continuation maintenance + 194 PS 2 patients second-line + 1,056 PS 0-1 advanced disease mesothelioma patients). Of note, the estimated 4,898 patients eligible for first-line treatment includes 10%-15% (N=490 to N=735) of patients who are EGFR mutation positive (Final scope, Afatinib EGFR positive locally advanced or metastatic NSCLC. ID556; Costing statement for TA258). In current clinical practice and in accordance with NICE guidance, EGFR positive patients would be eligible for erlotinib or gefitinib rather than pemetrexed. The maximum plausible estimate, revised by the NICE technical team and Lilly using the latest NLCA data, demonstrates that the eligible patient population is **6,803** and pemetrexed continuation maintenance should therefore be considered under the 'End of Life' supplementary criteria	Comments noted. The estimated size of the total population size for which pemetrexed has a licence has been updated. See section 4.26 of the FAD.

Comments received from clinical specialists and patient experts

No comments received

Comments received from commentators

Consultee	Comment	Response
Royal College of Physicians – ACD3	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with regard to the above ACD consultation. We are pleased that this has taken into account the comments we previously submitted regarding the double counting of patients. However, we note that the committee remains unwilling to consider the 'real life' numbers of patients treated with pemetrexed in the second line setting (paragraph 4.24). The rationale proposed for this view is that the calculation of patient numbers should be potential (rather than actual) when determining whether the technology being appraised is applicable to 'a small population for an end of life treatment'. Nonetheless, even if this argument is accepted, second line pemetrexed is not NICE approved and, therefore, is not available through NHS treatment (although it is available on the CDF). As such, our experts fail to understand how this can be included as a potential group of patients who might be treated with pemetrexed in the UK where NICE guidance governs treatment pathways. We would argue that this falsely inflates potential patient numbers to an extent which prevents pemetrexed being considered for 'a small population for an end of life treatment', and that this may ultimately impact on the final decision made about the technology.	Comments noted. The estimated size of the total population size for which pemetrexed has a licence has been updated. See section 4.26 of the FAD.

Consultee	Comment	Response
Royal College of Physicians – ACD3	That important point aside, the main reason for the negative ACD would appear to be the high ICER per QALY gained. We are aware that there has been much discussion between the manufacturer's health economists and the committee with regard to the methods used to determine this.	Comment noted

Comments received from members of the public

No comments received