NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (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	Comment	Response
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document and evaluation report for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation	Comment noted
Royal College of Nursing	Nurses working in this area of health have reviewed the Appraisal Consultation Document of the technology appraisal of Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]. Feedback from them suggests that there are no comments to submit at this stage on behalf of the Royal College of Nursing. Thank you for the opportunity to review the document and we look forward to participating in the next stage of the appraisal.	Comment noted
Royal College of Physicians	Please take this email as confirmation that the NCRI, RCP, RCR, ACP, JCCO have had sight of the response to the ACD submitted by the clinical expert Dr Yvonne Summers. The organisations wish to fully support the comments made.	Comment noted
Royal College of Pathologists	Please note that the Royal College of Pathologists has no comments to make at this stage.	Comment noted

Consultee	Comment	Response
Lilly	Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on pemetrexed for the continuation maintenance treatment of non-squamous NSCLC.	Comment noted
	Lilly are pleased that the Appraisal Committee have recognised the clinical benefit that pemetrexed continuation maintenance offers to patients. However, Lilly are disappointed that the Committee did not provisionally recommend pemetrexed for non squamous non-small cell lung cancer in the continuous maintenance setting after recommendations supporting 1st line and switch maintenance use (TA181 and TA190).	Comments noted
	A negative recommendation for continuation maintenance could lead to variation or inequity in the treatment of essentially the same group of patients, differing only in terms of their first-line regimen (pemetrexed or non-pemetrexed in combination with platinum). This decision relates to a small number of eligible patients (n=588) but has the potential to create confusion in oncology centres that are already providing pemetrexed for patients with non-squamous NSCLC.	The Committee considered issues related to the equality legislation and the requirement for fairness, See section 4.28 of the FAD.
	Pemetrexed continuation maintenance enables patients to maintain the benefit of best-practice first-line treatment and further extend survival in patients with non-squamous NSCLC. The combined impact of first-line and maintenance therapy has extended the life of patients in a disease where, prior to the introduction of pemetrexed, patients survived on average less than 12 months from diagnosis. Pemetrexed continuation maintenance is an effective treatment which improves one year lung cancer survival and could improve five year survival, key priorities for the Government (NHS Outcomes Framework 2012/2013).	The Committee considered the clinical effectiveness and concluded that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.

Consultee	Comment	Response
Lilly	**Implementation considerations** The Committee's preliminary recommendations on pemetrexed continuation maintenance would have the unacceptable consequence of requiring that pemetrexed treatment be withdrawn from patients who are deriving an important benefit from pemetrexed/cisplatin first-line therapy and for whom continued pemetrexed treatment to maintain that benefit is a logical treatment strategy. When negative NICE guidance is issued, NICE seeks to avoid the withdrawal of treatment from patients currently benefitting from such therapy, by including a standard statement to that effect in all its guidance. The Committee's recommendation for pemetrexed, currently under consultation is inconsistent with that approach and raises the same ethical issues that NICE is generally concerned to avoid through its standard statement. We believe that this is an important matter that should be taken into account by the Committee before guidance is finalised.	The recommendations in this appraisal relate to pemetrexed as a maintenance treatment following induction therapy with pemetrexed and cisplatin and not pemetrexed as a first line therapy. NICE has previously issued a positive recommendation for pemetrexed as a first line therapy in TA181 'Pemetrexed for the first-line treatment of non-small-cell lung cancer' Comments noted. The text has been amended within the FAD to include the word 'maintenance'. See section 1.2 of the FAD.
Lilly	**Application of the supplementary advice on 'End of life' in the context of the size of the cumulative patient population eligible for pemetrexed** We do not believe the approach followed by the Committee when determining the population size is fair or reflects the proposed use of pemetrexed. While we accept the Committee's estimates of eligible population size for first-line non-squamous NSCLC (n=4555, ACD paragraph 4.22) and for mesothelioma (n=1606, ACD paragraph 4.25), we believe that 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=1500, ACD paragraph 4.24) due to misinterpretation of the clinical specialists' comments during the Committee meeting. In addition, we do not agree with the inclusion of patients in the switch maintenance setting who have not been exposed to pemetrexed in the first-line setting (n= 565 calculated from ACD paragraph 4.23).	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.

Consultee	Comment	Response
Lilly	By double-counting patients receiving maintenance, as documented in paragraphs 4.23 and 4.24, the Committee has applied the 'End of life' advice in a way that is inconsistent with the way that it has been applied in other appraisals. The Committee included patients eligible for switch maintenance, which is inappropriate as these patients by the nature of the authorised indication must have not received pemetrexed first-line to be eligible for maintenance. In addition, we do not believe continuation maintenance, should be included as it is essentially an extension of first-line treatment to disease progression in the same patient.	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.
Lilly	Pemetrexed should qualify for 'End of Life' consideration in terms of the small population criterion. According to our calculations (see Appendix 1), the total eligible population that the Committee should consider is n=6184, which includes n=1606 for mesothelioma, n= 4555 for PS 0-1 first-line NSCLC and n=23 for PS 2 second-line NSCLC. Even working with the intent of the End of Life criteria by including the continuation maintenance population of n=588, the total eligible population would be n=6772, which falls beneath the 7000 threshold. The Committee may wish to note that the population of first-line patients, if estimated in accordance with the licensed indication, would in fact exclude EGFR mutation positive patients (~15%) who would not receive platinum-based chemotherapy, thus resulting in an even lower number of eligible patients.	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.
Lilly	For the benefit of the Appraisal Committee, we have depicted our calculations in Figure 1 below. Since the population size is a crucial criterion for consideration under the EOL supplementary advice, we would like to request that Figure 1 be projected on screen for Committee members at the second Appraisal Committee meeting to facilitate understanding and inform the Committee's discussions around these numbers (a powerpoint presentation with the figure is also enclosed).	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26. As requested figure 1 was presented to the Committee

Consultee	Comment	Response
Lilly	**Economic considerations** The committee considered that pemetrexed was not cost-effective as continuation maintenance therapy when compared to Best Supportive Care. The cost-effectiveness of pemetrexed in the continuation maintenance setting was estimated in the Manufacturer's submission to be £47,576 whilst the estimate in the ACD was given as £76,300, dependent upon various changes to underlying methodology and assumptions suggested by the Evidence Review Group (ERG). We believe that both the methodological approach utilised within the model structure, and the basecase assumptions were appropriate and accurate and have led to a plausible, realistic ICER within our submission. We believe the modelling approach merits further elaboration, in order to reassure the Committee that the most probable estimate of incremental cost effectiveness falls within the range of £47K - £59K. The main concerns relating to the economic model, as documented in the ACD, relate to the following, which we will explore in turn: a) the approach to modelling of progression-free survival (PFS) and overall survival (OS) and extrapolation beyond the time period of the clinical trial and b) the plausibility of some of the assumptions and inputs in the economic model.	Comments noted Comments noted Comments noted
Lilly	**Modelling of overall and progression free survival** In terms of impact upon the final incremental cost per QALY, the methods used to estimate survival have the greatest single effect upon cost-effectiveness ratios. The ERG suggest that in the original submission Lilly overestimated the treatment effect of pemetrexed by using i) a misspecification of the survival function (i.e. gamma versus exponential) and a single parametric function to generate OS estimates for both arms simultaneously, rather than a different survival function for each arm in the trial and ii) in the estimate of the post-progression treatment effect within the extrapolation.	Comments noted. The Committee did not find any reason for basing its decision on overall survival on anything other than the PARAMOUNT data, which did not show any evidence of a post-progression benefit for pemetrexed over placebo. See section 4.15 of the FAD.

Consultee	Comment	Response
Lilly	i) With regards to the *misspecification of the survival function* we believe the original choice of gamma is more appropriate than the suggested exponential for the following reasons (Appendix 2 has further details): • Lilly conducted a systematic approach to survival analysis, following the guidance provided in the NICE Technical Support Document (Latimer 2011). • The chosen survival function better reflects the observed data in the PARAMOUNT Clinical trial. Evidence to support this argument is explained in Appendix 2 by showing the smoothed hazard plots. • Standard statistical methods designed to assess the goodness of fit also support the choice of gamma over exponential distributions. • Residual plots provided by the ERG (Figures 8 and 9, ERG Report, p59, Jan 2013) show that the gamma distribution is a better fit than the exponential over the whole trial duration and in particular towards the end of the trial where the extrapolation begins.	See above and section 4.15 of the FAD.
Lilly	On the basis of the above we believe that, by all conventional assessments, the gamma distribution offers the best fit of the observed data compared to the exponential model and provides a clinically plausible long-term survival estimate.	See above and section 4.15 of the FAD.
Lilly	With regards to the *use of a single parametric function* to generate OS estimates for both arms simultaneously, the ERG has suggested that the approach used in the original submission was not appropriate based upon a belief that survival trends observed in the latter part of the trial are suggestive of a constant hazard assumption meaning there should be no difference in treatment effect between the two treatment arms Whilst we agree that it is necessary to establish appropriate survival projection, we believe that this projection should not be focused upon data which are likely to be subject to the greatest level of uncertainty at the end of the trial and that a projection based on a fully fitted survivor function (as per the original submission), using all the observed data from the clinical trial, is likely to be more reliable.	See above and section 4.15 of the FAD. See above and section 4.15 of the FAD.

Consultee	Comment	Response
Lilly	In addition and to further support the Committee's deliberation on this point we have conducted additional statistical tests, which show that the proportional hazard assumption is not violated and therefore reinforce that the original choice of a gamma model which used a single parametric function for both arms in the model is valid and appropriate.	See above and section 4.15 of the FAD.
Lilly	ii) The OS treatment effect in the model is based upon the within-trial period, taking account of both the pre-progression and post-progression periods. Uncertainty arises in relation to the treatment effect only in the extrapolation period and we therefore have to make an assumption in the model to this effect. By definition, no one knows with certainty what happens to the treatment effect after the trial ends. This is a question of clinical plausibility, which should take into consideration: biological plausibility for continued benefit. During the development of the model, (and supported during the Committee meeting), clinical experts suggested that it was biologically plausible that pemetrexed could alter the tumour such that treatment benefit continues post-progression. Therefore this benefit was included within the model. Whilst we do not have data specifically for pemetrexed, or for lung cancer, there is an emerging body of evidence that supports a hypothesis of biological plausibility for a continuing treatment effect post-trial for other cancers. It has been shown in advanced prostate and renal cell cancers (Stein et al 2009; Stein et al 2011) that part of the treatment effect is due to a change in growth rate of the residual tumour after treatment is stopped, i.e. the tumour has been fundamentally altered during treatment so that the tumour grows more slowly and survival is prolonged after the treatment is discontinued. We therefore believe that continued OS treatment effect in the extrapolation period is plausible and that modelling no beneficial effect is over conservative and likely to be inaccurate.	See above and section 4.15 of the FAD. The Committee considered the findings in the two Stein et al papers did not support an extended benefit of chemotherapy following disease progression. See section 4.15 of the FAD

Consultee	Comment	Response
Lilly	**Model inputs and assumptions** In the estimation of incremental cost-effectiveness, there is always a range of appropriate model inputs and parameterisation which can lead to a range of plausible basecase scenarios. Many of these were included within an extensive range of deterministic sensitivity analyses for alternative plausible scenarios in our original submission, but below we have adjusted the model based upon the suggestions of the ERG, to help inform the committee in their considerations. In the revised basecase we have incorporated the ERG's suggestions which were considered to better reflect UK clinical practice (e.g. monitoring costs, cost by BSA), all but one of the adjustments to the pemetrexed-related costs and the half-cycle correction. Please refer to Table 1 in Appendix 2 for full details of all the amendments incorporated to the basecase.	Comments noted. The Committee welcomed the manufacturer's revised base-case.
Lilly	When these changes are incorporated within the model, the revised estimate for incremental cost effectiveness is £59K providing the committee with a plausible and realistic range of ICERs to consider, from £47K - £59K.	Comments noted.
Lilly	Further evidence and rationale to support Lilly's survival modelling approach, a more detailed response to the points raised by the Committee and the ERG in relation to the economic model, and a summary of changes made to inputs and assumptions implemented in the revised basecase analysis are provided in Appendix 2.	Comments noted.

Consultee	Comment	Response
Lilly	In conclusion, pemetrexed continuation maintenance is a well-tolerated and effective treatment option that will improve survival in patients suffering from a disease with poor prognosis, a key national Government priority. We strongly believe that pemetrexed in the continuation maintenance setting should be assessed under the End of Life criteria. The revised estimates for incremental cost-effectiveness of a robust economic model provide the Committee with a range of plausible and realistic ICERs between £47K and £59K. Lilly do not consider it the best option for the NHS to introduce a complex patient access scheme (PAS), within the context of increasing NHS productivity, when the eligible population for pemetrexed as continuation maintenance treatment is so very small (n=588) and other key indications are all recommended by NICE in England and Wales.	Comments noted. The Committee was persuaded that the most plausible ICER was approximately £82,000 per QALY gained. See section 4.17 of the FAD.
Lilly	We hope the information presented in our response will help the Appraisal Committee support a recommendation for pemetrexed as continuation maintenance treatment, a recommendation that will be clinically consistent with NICE's previous decisions and will avoid confusion in the implementation for patients in the real life clinical setting.	Comments noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Dr Yvonne J Summers - On behalf of NCRI Lung CSG and the Royal College of Physicians	I was very disappointed to read the contents of the ACD regarding Pemetrexed maintenance in NSCLC and would ask that the following points be drawn to the attention of the committee when it reconvenes on Wednesday 27th March 2013: 1. There has been much discussion about the various models used by the manufacturer and the ERG and extensive debate over the survival benefit gained in the pemetrexed arm in the post progression period. In section 4.16, page 23, line 1, the document states, “The Committee heard from the clinical specialists that a continued benefit of pemetrexed over best supportive care after disease progression would not be expected”. Whilst we could not explain why there was an improvement in outcome for patients on the pemetrexed arm of the trial in the post progression period, the patient derived data from the PARAMOUNT study shows a greater improvement in overall survival compared to progression free survival (2.9 versus 1.3 months respectively). Whether or not this finding is expected these are the results that were observed and cannot be discounted. With regard to end of life supplementary advice and in particular reference to the small patient population calculations (section 4.20) I would make the following comments: 2. With regard to end of life supplementary advice and in particular reference to the small patient population calculations (section 4.20) I would make the following comments:	Comment noted. Comments noted. See FAD section 4.15. The Committee noted the ERG’s Kaplan-Meier analysis of post-progression survival which indicated that for the 2 trial arms, survival corresponded very closely. The Committee was not persuaded that the data supported a continued benefit for pemetrexed beyond progression, compared with placebo.

Nominating organisation	Comment	Response
J Summers - On behalf of NCRI Lung CSG and the Royal College of Physicians	**Maintenance**. There was a lengthy discussion at the committee meeting about why there has been virtually no uptake of pemetrexed maintenance following non-pemetrexed doublet 1st line chemotherapy since NICE approved its use in June 2010 (TA190). It was discussed that patients with non-squamous NSCLC who were PS 0-1 and fit for pemetrexed and cisplatin 1st line are receiving this treatment preferentially, thus making them ineligible for pemetrexed maintenance under current guidelines. The fact that so few patients have received pemetrexed maintenance since June 2010 gives us almost 3 years of data which confirms that patients who are not fit for cisplatin and pemetrexed 1st line therapy, but receive another 1st line treatment, are extremely unlikely to be fit for maintenance therapy for the same reasons that excluded them from pemetrexed treatment in the first place (i.e. poor PS, co-morbidities, etc.). There is no evidence in the literature that any significant proportion of PS 2 NSCLC patients become PS 0-1 after chemotherapy. It is therefore unreasonable to assume as is stated (section 4.23, page 27) "As there was a similar number of such patients receiving first-line chemotherapy which did not contain pemetrexed, there was likely to be a similar number of patients eligible for 'switch maintenance' therapy". I would strongly dispute this point and would suggest that the original estimate of 535 patients is closer to a correct estimate of potential patient numbers.	The Committee noted comments received during consultation and revised the population estimates. The Committee accepted the manufacturer's revised estimate that 588 patients would be eligible for pemetrexed continuation maintenance. See section 4.23 of the FAD.

Nominating organisation	Comment	Response
Dr Yvonne J Summers - On behalf of NCRI Lung CSG and the Royal College of Physicians	**2nd Line treatment**. Making calculations from the LUCADA database is welcomed, as this is the most accurate reflection of UK practice, however in making an estimate of numbers of patients potentially suitable for second line pemetrexed treatment, there is no reference to this valuable resource having been used by the committee (section 4.24, page 28). Instead there is a rough calculation which suggests that if a third of PS 2 patients get 1st line treatment, then this number is approximately 1500 and then **ALL** of these 1500 patients are then suitable for 2nd line pemetrexed. This conflicts directly with the LUCADA database for 2011 which shows that there are 1762 PS 2 patients with stage IIIB/IV non-squamous NSCLC and, of these, 462 had 1st line chemotherapy. In UK practice 25% of PS 0-1 patients receive 2nd line chemotherapy (and in PS 2 patients this is probably closer to 5%). Even if 25% were taken as the proportion receiving 2nd line therapy, the number would be 115. At the committee meeting there was discussion that NICE has not approved the use of 2nd line pemetrexed for patients with NSCLC and so the actual numbers of patients receiving 2nd line treatment in the UK is close to zero.	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information. Following consultation comments the Committee revised its estimated number for patients eligible to receive second-line pemetrexed. See section 4.24 of the FAD.

Nominating organisation	Comment	Response
Dr Yvonne J Summers - On behalf of NCRI Lung CSG and the Royal College of Physicians	In summary, it would appear that the total number of patients potentially eligible for any pemetrexed treatment that the committee came to was 8761, but my adjustments would reduce this to 6811. I would hope that in view of the above information, the question of whether pemetrexed is considered to fulfill the end of life criteria would be revisited. Furthermore, I would like to take this opportunity to emphasise that pemetrexed maintenance treatment is of substantial benefit (3 months improvement in survival with maintained quality of life) to a selected small number of lung cancer patients for whom the outcome is so poor (median survival 9 months). I hope that these comments are helpful in reaching a final decision.	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.
Dr Riyaz Shah – Nominated by Lilly	I do not feel that the provisional recommendations are sound or a suitable basis for guidance to the NHS. My main concern regards the conclusion that this indication could not be considered under the supplementary advice to the Committee on end of life treatments (4.26). The Committee calculated this population to be in excess of 8000, however my calculations suggest that this is a gross overestimate. I agree that the National Lung Cancer Audit 2012 (NLCA2012) provides the most robust database upon which to base population calculations. While not all lung patients are captured by this database, it does capture all patients discussed at MDM?s and therefore provides the most accurate estimation of the ?real? and ?treatable? population. My rationale is detailed in section 4.	Comment noted. Comments noted. Comments noted.

Nominating organisation	Comment	Response
Dr Riyaz Shah – Nominated by Lilly	In para 4.23 there is significant consideration of the switch maintenance strategy. I feel that this is misleading. Assuming that a patient has Stage IIIb/IV non-squamous non small cell lung cancer and a PS of 0-1, the correct treatment would be cisplatin and pemetrexed. This is NICE approved. There may be some patients, in whom pemetrexed is contraindicated however, in my clinical experience that is a very rare phenomenon. It is important that the committee appreciate that switch and continuation maintenance are not applicable to separate subgroups of patients. These treatment strategies relate to potential pathways for the same subgroup of patients.	The Committee noted comments received during consultation and revised the population estimates. The Committee accepted the manufacturer's revised estimate that 588 patients would be eligible for pemetrexed continuation maintenance. The Committee concluded that the total population for both continuation and switch maintenance treatment would be approximately 1500. See section 4.23 of the FAD.

Nominating organisation	Comment	Response
Dr Riyaz Shah – Nominated by Lilly	NICE estimate 6698 patients with NSCLC stage IIIB or IV and a PS of 0-1. 68% are nonsquamous giving a population of 4555. NLCA2012 shows about 55% of these patients are treated with chemo, giving a population of 2500 who are actually eligible for cisplatin + PEM first line and 1500 may go on to maintenance PEM. The population eligible for first line + maintenance is 2500 + 1500 = 4000. Does the manufacturer have sales data that would help estimate the 1st line population size? Adding the group of patients eligible for second line PEM is misleading. The second line license is old and predates that data showing its benefit in the non-squamous subgroup. The trial (Hanna et al. J Clin Oncol 2004) is based on patients recruited between 2001 and 2002. This a historical trial. There is no evidence supporting the role of PEM second line in patients pretreated with first line PEM let alone those receiving maintenance PEM. Second line PEM is not cost effective, not NICE approved and has no defined commissioned pathway. My calculations suggest the total population size eligible for PEM is no more that 5600 (2500 first line + 1500 maintenance + 1600 meso). Or 7100 if including second PEM.	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information. Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.
Dr Riyaz Shah – Nominated by Lilly	I feel that adequate importance was not given to the clinical experts opinions that maintenance chemotherapy is a highly effective strategy for a small subgroup of patients. The experience from the cancer drugs fund would indicate that only a small number of patients are being offered this treatment within regions where no financial barrier exists (i.e. the cancer drugs fund in that area have a blanket policy to approve all requests for maintenance chemotherapy). This suggests that even with no barrier to access, oncologists are being highly selective and offering this to the select subgroup of patients identified within the PARAMOUNT trial.	Comments noted.

Nominating organisation	Comment	Response
Dr Riyaz Shah – Nominated by Lilly	Pemerexed is coming close to the end of its patent. I don't know the exact dates however, the price of this drug is likely to drop substantially after that point. This will fundamentally alter all of the cost effectiveness calculations. It would be helpful if NICE could review their guidance on this drug in a timely manner after that point.	Comments noted. It is anticipated that this will be taken into account when setting a review date.

Comments received from commentators

Commentator	Comment	Response

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	4.23	From a working clinical perspective, the majority of patients who are diagnosed with Non Squamous NSCLC generally receive Pemetrexed with Capsulation or Carboplatin. This group would therefore be eligible, if fit enough, for Pemetrexed maintenance therapy. Patients who receive any other chemotherapy agent other than Pemetrexed ie Gemcitabine, Paclitaxel (with Cisplatin or Carboplatin) would not, as far as our understanding goes, be eligible for Pemetrexed maintenance therapy. Therefore the analysis from the appraisal, which mentions switch maintenance, is not relevant. The NLCFN would therefore assume that the numbers of patients eligible are greatly reduced. For the End of Life Criteria this is very important to consider.	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 1	4.24	Also relevant to the above comments, it could be recognised that those patients eligible for second line Pemetrexed have been overestimated. You have stated that patients who did not receive Pemetrexed as induction or maintenance of would be potentially eligible for second line chemotherapy following disease progression. However, the number of patients (1500) that you have quoted who might be eligible for second line therapy (one third of PS 2) appears high from our perspective. In addition we think that the point raised in 4.23 needs clarification as if patients have had Pemetrexed therapy first line then they would not be eligible second line. This again significantly impacts total patient numbers and hence eligibility of End of Life Criteria.	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.

Role*	Section	Comment	Response
NHS Professional 1	4.10	Whilst we recognise that you have focused on only one mode of surveillance with CT follow up based on the Paramount study we are sure that there will be clinical variation (based on clinician preference) to detect recurrence. Chest x-rays can be utilised as routine in follow up with CT requested if there are concerns from CXR or patient reported symptoms.	Comments noted. Please see section 4.10 of the FAD for the Committee's conclusions on CT scans.
		Patients on maintenance treatment could be followed up in Lung Cancer Nurse Specialist led clinics rather than the traditional medical led clinic. Lung Cancer Nurse Specialists are skilled practitioners who will know the patient well and are highly likely to detect early signs of recurrence through recognition of concerning symptoms. Patients have access to Lung Cancer Nurse Specialists for advice and access to be reviewed in clinic at any time in event of problems with disease progression often identified via this line of follow up. These modes of follow up have been identified as effective in terms of detecting recurrence and acceptable to patients. Internal audits of practice within Lung Cancer Units have demonstrated this. This again will reduce the cost of providing Pemetrexed as maintenance therapy.	Comments noted.
		We would also like to highlight the importance of the quality of life for patients receiving maintenance Pemetrexed therapy. From our perspective maintenance therapy will potentially delay the onset of distressing symptoms, reduce hospital visits, a reduction of inpatient stays and a reduction of prescriptive medications (and associated costs). This is hugely important from a nursing perspective and takes into account the associated impact on community services.	Comments noted. The Committee was aware of comments received from a patient group describing the limited life expectancy of people with NSCLC and of the importance to patients and their families of the availability of additional active therapy options.

Role*	Section	Comment	Response
NHS Professional 1	General	Our final comment is with regards to the historical lack of treatment options for patients with lung cancer. The initial studies into lung cancer chemotherapy did not show major differences in survival but the clinical community has gradually increased its knowledge, understanding and clinical application in the delivery of chemotherapy and novel agents. We welcome new agents into the practice. Pemetrexed has proven to be an effective chemotherapy agent in the first line setting, well tolerated, with the potential to deliver good response rates. We would like to see this available as a maintenance therapy to offer as a therapeutic option for our patient population and hope that you take our comments into consideration.	The Committee reviewed the data available on the clinical and cost effectiveness of pemetrexed, having considered evidence on the nature of non-squamous NSCLC and the value placed on the benefits of pemetrexed maintenance treatment following pemetrexed and cisplatin induction therapy by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources
NHS Professional 2	Section 1	Several errors in the preliminary recommendations reduce the cost effectiveness and have overestimated the patient numbers (excluding end of life consideration).	Comments noted. Please see section 4.21 to 4.26 of the FAD for a full discussion around patient numbers.
NHS Professional 2	Section 1	Worryingly comments on age eg 3.14,4.6 etc reveal a bias for doubting the applicability of the results to our patient population, there is no evidence that age is a prognostic nor predictive factor for NSCLC chemotherapy.	The Committee accepted that pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin (and with a performance status of 0–1) provides a statistically significant gain in progression-free survival and overall survival compared with placebo.
NHS Professional 2	Section 1	The economic assessments eg 3.20 3.21, 4.15, based on the post hoc use of an adjusted model when there was no baseline patient imbalance and PFS secondary calculations eg 3.19 with the attendant observer variability, rather than the definitive OS endpoint are a very questionable, unreliable approach.	Comments noted.

Role*	Section	Comment	Response
NHS Professional 2	Section 1	There is double counting 4.21 - 4.23, for the patient number likely to receive pemetrexed as switch maintenance would not be prescribed as first line pemetrexed platinum is given routinely in the UK.	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information.
NHS Professional 2	Section 1	No pemetrexed is used 2nd line 4.24 as it is not approved by NICE and counting these invisible patients is a specious argument which is clinically meaningless .	Please see above and section 4.21 of the FAD.
NHS Professional 2	Section 1	Using currently available data the expected total patient population would be <8000 ~7000.The appraisal is likely to be positive for providing a more objective, clinically meaningful approach is taken	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.
NHS Professional 2	Section 2	Pemetrexed is an important new cytotoxic which has benefitted advanced NSCLC patients in terms of clinically important increases in overall survival with no quality of life detriment due to a milder side effect profile. Extending the benefits of pemetrexed with continuous maintenance for people with advanced NSCLC would help reduce a serious unmet need	Comments noted.
NHS Professional 2	3.14	These comments are irrelevant as patients would only be treated if PS0 1, age is not prognostic, predictive, and stage IV has increased in trials because of the new TNM classification.	Comment noted

Role*	Section	Comment	Response
NHS Professional 2	3.16	Where is the evidence for ERG`s criticism based on the 8 parameters eg BSA	Additional information on these parameters is available in section 6.1.2 of the ERG report.
NHS Professional 2	3.17	Given there was no baseline imbalance insisting on an adjusted model equates to post hoc prejudicial fitting of data to an ERG preferred model	Comment noted
NHS Professional 2	3.18	Why use a common survival when the trial survival was so different, extrapolating at the end of the survival curves with ~30 patients overall introduces wider confidence limits and is more unreliable than using all the survival data from the start. The approach has no clinical value	For clarity, the common survival level refers to the point at which projection begins. Section 4.16 of the FAD provides further details. 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. 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.
NHS Professional 2	3.19	A plausible explanation is selection of more slowly growing clones, the faster ones being more sensitive to CT.	Comment noted.
NHS Professional 2	3.21	Scenario 4 the post hoc reasoning for an adjusted model just because it reduces an assumed post progression survival, which in turn is based on CT scan interpretation introduces many unnecessary assumptions and questions the validity and clinical relevance of such an approach	The frequency of monitoring (CT scanning) is an assumption within the economic model which impacts on the cost of pemetrexed treatment. The quantity of time spent in post progression survival is independent of this assumption. The Committee did not find any reason for basing its decision on anything other than the PARAMOUNT data, which did not show any evidence of a post-progression benefit for pemetrexed over placebo.
NHS Professional 2	4.6	Only PS0/1 patients entered the trial and PS01 non trial patients would be expected to behave similarly	Comment noted

Role*	Section	Comment	Response
NHS Professional 2	4.8	It should be noted that in Paramount EQ5D was used a generic questionnaire and not sensitive to lung cancer specific symptoms as in FACT L where there was an improvement in the switch maintenance trial.	Comments noted.
NHS Professional 2	4.10	Follow up appointments are the same, every 6-8 weeks as recommended in guidelines but is often much shorter due to the rapid progression <2 months with serious symptom logy with a wait and watch policy, these patient need similar if not more hospital interventions. The median number of five pemetrexed cycles argues at the most one extra CT scan will be at a six week interval.	Comments noted. Within the manufacturers revised base-case the frequency of CT scans has been updated to once every 12 weeks. See section 4.10
NHS Professional 2	4.12	The trial data did show reduction in subsequent treatment in the pemetrexed arm particularly in the erlotinib 6% and docetaxel 6% treatments. Choosing t o disregard these data as non-significant where no such restriction exists in the economic adjusted analysis is untenable	Comments noted. Within the manufacturers revised base-case the differential rate of second-line chemotherapy has been removed. See section FAD section 4.11
NHS Professional 2	4.13	Disagree given the above.	See above
NHS Professional 2	4.14	There is no reason to use an adjusted model as no imbalance in the pre-treatment characteristics and age is not a prognostic independent significant factor The ERG`s post hoc analysis tagged onto the end of the survival curves will of course be less robust than examining the whole of the survival curve. The post hoc fitting of the ERGs adjusted model is unscientific and clinically inappropriate.	Comments noted. The Committee decided against using the manufacturer's projections for survival. See section 4.15 of the FAD.
NHS Professional 2	4.15	The cut points of 20% is reasonable clinically, larger numbers are always preferable to smaller numbers	Comments noted.

Role*	Section	Comment	Response
NHS Professional 2	4.20	It must be noted that in the UK pemetrexed is not used the second line setting, NICE guidance and therefore does not contribute to the patients actually treated in this end of life criteria	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information.
NHS Professional 2	4.23	Double counting, pemetrexed switch maintenance trial is no longer relevant, given the widespread UK use of 1st line pemetrexed Here market research data are used (although not used for the second line indication (below), zero in the UK. Therefore, 535 is a reasonable number.	See above and section 4.21 of the FAD
NHS Professional 2	4.24	Second line pemetrexed PS0-2 is not NHS funded, erlotinib which is funded would be used,	See above and section 4.21 of the FAD
NHS Professional 2	4.27	End of life criteria would be fulfilled if corrections to the assumptions re numbers are made	Comment noted. Even if the end-of-life considerations were taken into account, the most plausible ICER for pemetrexed maintenance following induction therapy with pemetrexed and cisplatin compared with placebo plus best supportive care was substantially higher than would normally considered to be a cost effective use of NHS resources

Role*	Section	Comment	Response
NHS Professional 3	3.7	It should be noted that no patients received 2nd line pemetrexed.	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information.
NHS Professional 3	3.14	The non-squamous NSCLC group occur in a younger, female predominant, better performance status with fewer ever smokers. In my opinion the trial population is consistent with my patient population.	Comment noted.
NHS Professional 3	4.23	It is an incorrect assumption to state that an equal number of patients will be eligible for switch maintenance. The majority of patients will be continuous maintenance	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.

Role*	Section	Comment	Response
NHS Professional 3	4.24	This assumption is grossly flawed. Note my earlier comment re 3.7	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information.
NHS Professional 3	4.25	This estimate is grossly flawed as a significant proportion of patients are PS 2 or worse and so unfit for chemotherapy.	Comments noted. The estimated size of the eligible population for pemetrexed has been updated within the FAD, see sections 4.21 to 4.26.
NHS Professional 3	4.26	Based on my comments I request that the committee reconsider this point.	Comment noted.
NHS Professional 4	1.1	Unfortunate grammar in wording of 1.1. On first reading it would appear that the guidance is recommending pemetrexed for use in squamous cell tumours. I know you have to use licenced indication but not at the expense of clarity and reasonable English. My other comments fed back to NCRI CSG so not included here.	Comments noted. As highlighted we have used wording which corresponds with the licensed indication. This avoids any ambiguity between our recommendation and what is in the MA. In addition, it provides consistency with the wording in TA190, which also refers to ‘other than predominantly squamous’ as per the marketing authorisation.

Role*	Section	Comment	Response
NHS Professional 5	1.1	1.1 Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than predominantly squamous cell histology in people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin. The wording of this paragraph can be interpreted as implying that Pemetrexed maintenance is recommended for squamous cell histology in non-progressing cases. This is clearly not the case and the wording should be amended to avoid confusion.	Comments noted. We have used wording which corresponds with the licensed indication. This avoids any ambiguity between our recommendation and what is in the MA. In addition, it provides consistency with the wording in TA190, which also refers to 'other than predominantly squamous' as per the marketing authorisation.
NHS Professional 5	Section 2	The demonstration of the specific activity of pemetrexed in nonsquamous cell histology NSCLC is, I believe, a significant advance in the management of this unfortunate group of patients. I say this as a medical oncologist who has published trials in this field over more than 20 years. It is an agent that is tolerated much better than competitors and, remarkably, is associated with almost no cumulative toxicity. Thus these patients, who include the life-long non-smoking lung cancer cases, are enjoying longer survival with fewer sife-effects.	Comment noted.

Role*	Section	Comment	Response
NHS Professional 5	Section 4	There are, I believe errors in the calculation of population sizes for Pemetrexed in 4.24. Since the data for second line therapy, switch maintenance and continuation maintenance became available at different times over the last few years an assumption has been made in the ACD that all three settings might be appropriate for an individual patient. This is not the case. Firstly, the patients likely to be offered continuation maintenance will not have been eligible for switch maintenance and vice versa, so in practice they will be the same 500 or so patients. These days, with the increasing use of first line Pemetrexed+cisplatin in non-squamous NSCLC they will all be offered continuation maintenance if eligible and therefore will not ever be eligible for switch maintenance. Similarly, patients who have had 1st line pemetrexed will not be receiving 2nd line with the same drug whether or not they have had continuation maintenance. So here again there has been double-counting. I believe this should make a significant reduction to the total number of patients eligible for, and receiving the drug.	The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. The Committee understood that the small patient population criterion was intended to recognise the long-term benefits to the NHS of innovation under these circumstances. The Committee was aware that, for this reason, it was appropriate to add the potential populations for all indications covered by the marketing authorisation together rather than consider them on the basis of actual use. See section 4.21 of the FAD for more information.

Summary of comments received from members of the public

Theme	Response