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[redacted]

Tel: [redacted]

HTA and Health Outcomes

Medical and Product Information: [redacted]

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Meindert Boysen
Programme Director, Technology Appraisals
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
1st Floor
10 Spring Gardens
London
SW1A 2BU

Pemetrexed for maintenance treatment of non-squamous non-small-cell lung cancer [ID489]
Lilly response to Appraisal Consultation Document (ACD)

Dear Meindert

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on pemetrexed for the continuation maintenance treatment of non-squamous NSCLC.

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).

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.

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).

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pemetrexed continuation maintenance would have the unacceptable consequence of requiring that pemetrexed treatment be withdrawn from patients who are deriving an important benefit from pemetrexed/cisplatin first-line therapy and for whom continued pemetrexed treatment to maintain that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.

Application of the supplementary advice on 'End of life' in the context of the size of the cumulative patient population eligible for pemetrexed

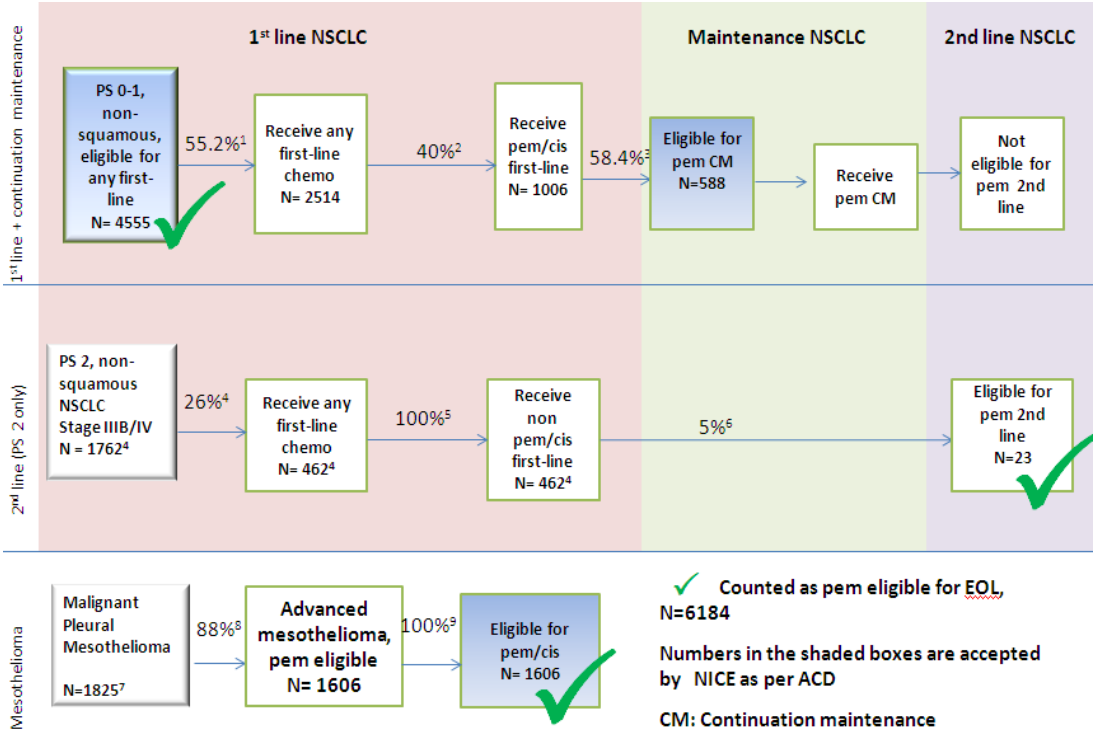
We do not believe the approach followed by the Committee when determining the population size is fair or reflects the proposed use of pemetrexed. While we accept the Committee's estimates of eligible population size for first-line non-squamous NSCLC (n=4555, ACD paragraph 4.22) and for mesothelioma (n=1606, 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).

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.

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.

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).

Figure 1. Patients eligible for pemetrexed across all indications - Lilly calculations



CM: Continuation maintenance; [1]Percentage of PS 0-1 Stage IIIB or IV NSCLC pts having chemotherapy, Page 39, NLCA Audit report 2012; [2] Pem/cis Share of market, GfK Market data Q4 2012; [3] Percentage patients eligible for pemetrexed continuation maintenance from the PARAMOUNT trial (Paz-Ares et al 2012); [4] Personal communication, Dr M. Peake: data extraction from National Lung Cancer Audit Database (2011 cohort); [5] Assumption; [6] Personal communication, Dr J Lester. March 2013; [7] NLCA Audit report 2012 page 8; [8] Pemetrexed ACD paragraph 4.25; [9] Assumption

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.

a. 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.

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.

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.

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.

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.

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.

b. 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.

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.

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.

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.

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.

Yours sincerely

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Enclosed:

1. Appendix 1 – End of Life
2. Appendix 2 – Detailed Cost Effectiveness response
3. List of factual inaccuracies
4. Powerpoint presentation with Figure 1
5. Confidential information checklist

References:

1. Department of Health. The NHS Outcomes Framework 2012/13 at a glance. http://www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131724.pdf

2. National Lung Cancer Audit report 2011. http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS_IC_Lung_Cancer_AUDIT_2011_Interactive_PDF_V1.0.pdf, accessed 15th August 2012.

3. Health and Social Care Information Centre. National Lung Cancer Audit report 2012. http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Lung-Cancer-National-Audit-Report-pub-2012.pdf

4. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012; 3(3):247-55.

5. Latimer N., NICE DSU Technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data, June 2011. http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis_finalv2.pdf

6. Stein WD, Gulley JL, Schlom J, et al. Tumour regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. Clin Cancer Res. 2011 Feb 1517(4):907-17.

7. Lilly data on file. GfK market research Q4 2012

8. Stein WD, Huang H, Menefee M, et al. Other paradigms: growth rate constants and tumour burden determined using computed tomography data correlate strongly with the overall survival of patients with renal cell carcinoma Cancer J. 2009 Sep-Oct:15(5):441-7.

9. Clinical practice based estimate of patients with PS 2 receiving second-line treatment. Personal communication. Dr. J. Lester. Consultant Clinical Oncologist. Velindre Cancer Centre, Cardiff, March 2013.

10. Data extraction from National Lung Cancer Audit (2011 cohort). Personal communication, Dr M. Peake. Consultant and Senior Lecturer in Respiratory Medicine, Glenfield Hospital, Leicester, March 2013.