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Dear Meindert

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

Thank you for the opportunity to respond to the third ACD consultation for pemetrexed in continuation maintenance treatment of non-squamous NSCLC.

We would like to focus our response on the calculation of the patient population eligible for consideration under the End of Life supplementary criteria.

End of Life supplementary advice: Calculation of the size of the pemetrexed-eligible patient population

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.

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.

Eligibility criteria for pemetrexed second-line treatment

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:

a. Receive non-pemetrexed first-line treatment
b. 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)
c. Experience disease progression after first-line treatment
d. Remain of adequate performance status (PS 2 or better) after disease progression so as to remain fit enough to be eligible for chemotherapy.

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.

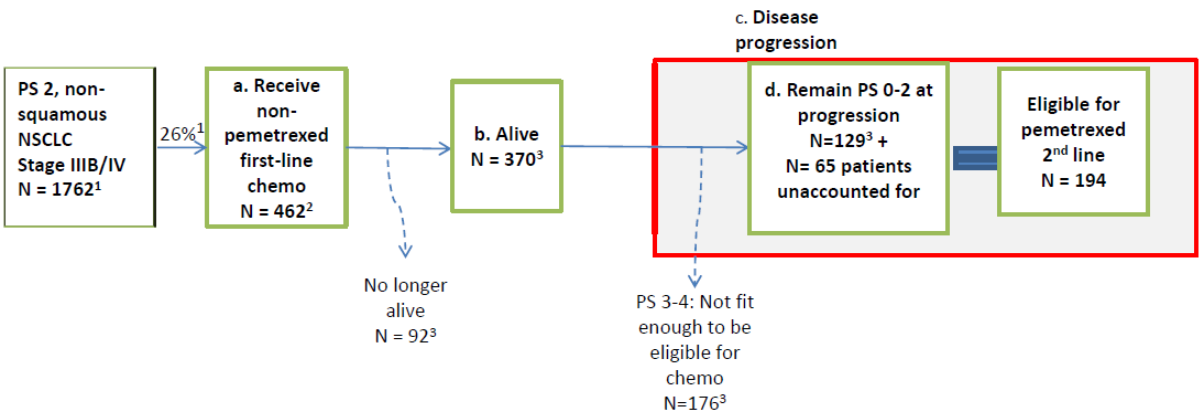
To summarise, the total number of patients eligible for pemetrexed treatment for all licensed indications, as accepted by the Appraisal Committee and mentioned in the 3rd ACD is as follows:

- 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

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).

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, [redacted]: 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, [redacted], 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).

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).

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.

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.

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.

Yours sincerely

[redacted]

Enclosed:
Appendix 1: Clinician responses to Lilly survey on PS 2 patients eligible to receive pemetrexed second-line treatment
Appendix 2: Considerations regarding cost-effectiveness

References:

1. 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.

2. 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.

3. National Cancer Drugs Fund. Quarterly figures – including notifications and Individual Cancer Drug Fund Requests (ICDFRs). April-September 2013/2014 http://www.england.nhs.uk/ourwork/pe/cdf/

4. NICE. Final scope. Afatinib for EGFR positive locally advanced or metastatic NSCLC. ID 556. May 2013.

5. NICE. Erlotinib for first-line treatment of locally advanced or metastatic EGFR mutation positive NSCLC. Costing statement. London: NICE; June 2012.

Appendix 1: Clinician responses to Lilly survey on PS 2 patients eligible to receive pemetrexed second-line treatment

Table 1. **Summary of responses to clinician survey* on number of patients eligible for pemetrexed second-line treatment**

			PS 2 at diagnosis, advanced non-squamous NSCLC after 1st line chemo		
Sr No	**Name**	**Designation**	**Died before progression**	**Progressed with PS 3-4**	**Progressed with PS 0-2**
1	[redacted]	[redacted]	30%	30%	60%
2	[redacted]	[redacted]	10%	10%	20%
3	[redacted]	[redacted]	25%	50%	25%
4	[redacted]	[redacted]	20%	30%	20%
5	[redacted]	[redacted]	15%	70%	15%
		Average	**20%**	**38%**	**28%**

*Based on responses from clinicians who responded to the survey and consented to have their details included in our response.

Appendix 2: Considerations regarding cost-effectiveness

The ERG conducted a landmark analysis, which examines the tails of the OS curves from 469 days (approx. 15.5 months) in the placebo arm and at 669 days (approx. 22 months) in the pemetrexed arm (Figure 2, reproduced from Figure 4, LRiG, Sept 2013). The ERG states that "visual examination appears to show very close correspondence" of the two arms in these tail sections (Section 2, page 3, LRiG, Sept 2013).

Figure 2 Calculation of OS gain directly from Kaplan-Meier analysis (Figure 4, LRiG, September 2013)

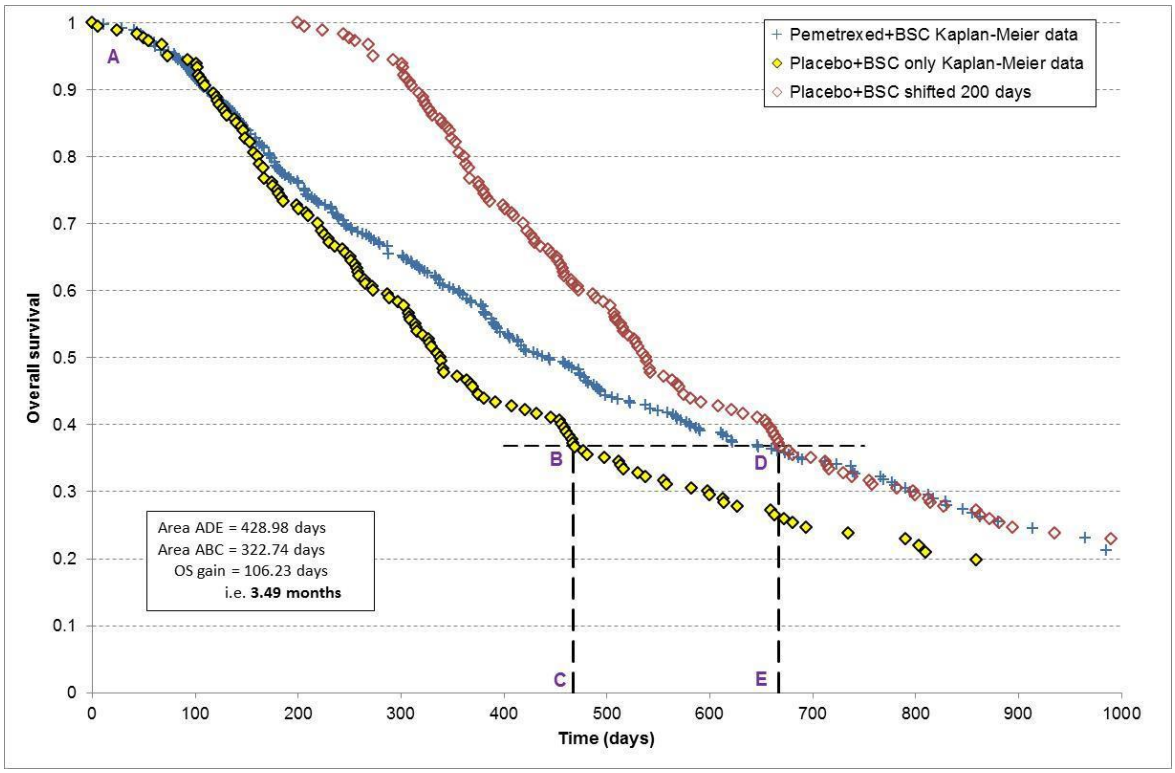
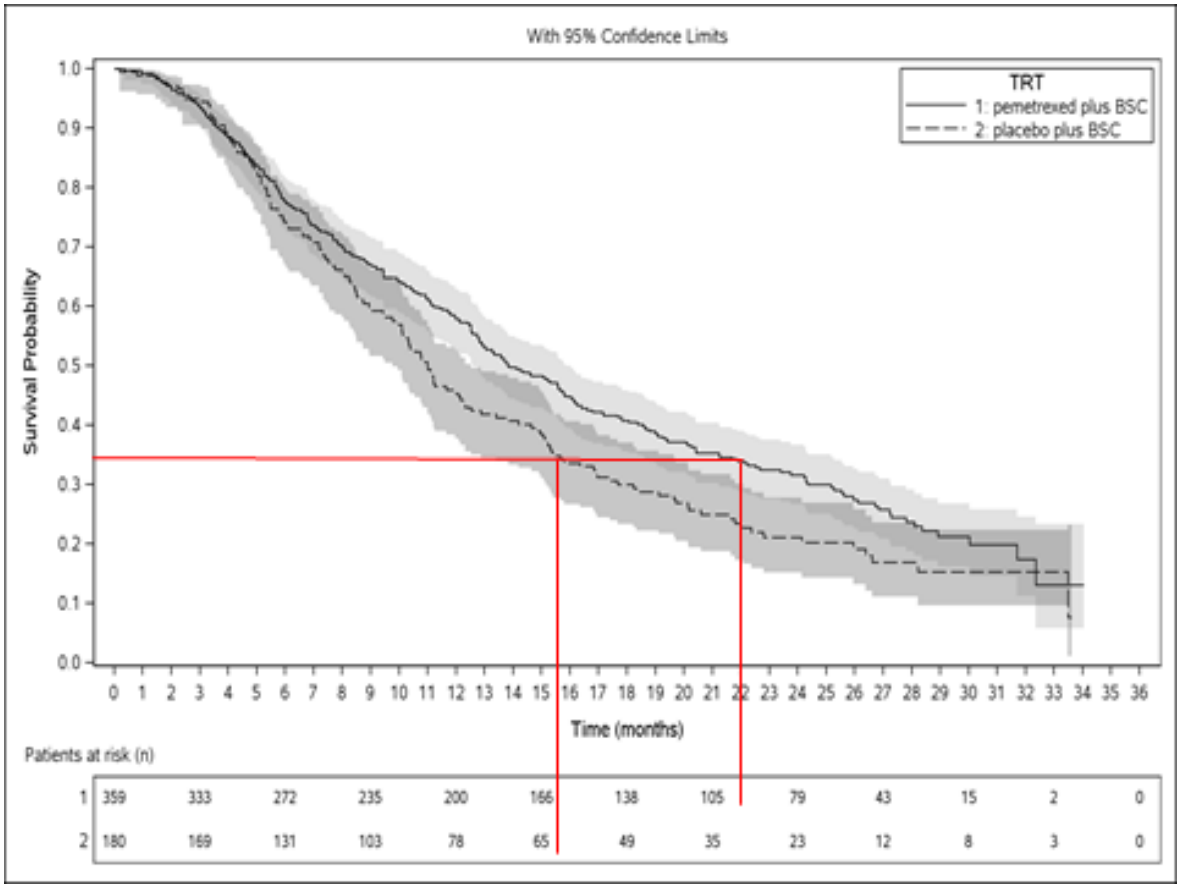


Figure 3 shows that the ERG's landmark analysis is restricted to data from approximately 100 patients for the pemetrexed arm and 63 patients for the placebo. During this period there were 29 deaths in the pemetrexed arm and 31 deaths in the placebo arm (Lilly economic model).

Figure 3 PARAMOUNT OS curves with 95% confidence limits and number of patients at risk



We would like to highlight a number of concerns with the ERG's landmark analysis and the associated re-estimated ICER:

- Log-rank test is not adequately powered
- Tails of the survival curves are unstable and give rise to uncertainty
- Re-estimation of the ICER is subjective

The implications of these three elements mean that the ERG's landmark analysis and revised ICER come with some level of uncertainty.

Log-rank test is not adequately powered

The ERG conducted a log-rank test on the tail sections of the OS curves to test the equivalence of the two curves and concluded that since the result was non-significant (p=0.754) this confirmed the visual assessment that the two arms correspond closely, i.e. that there is no difference in OS between the two arms.

The ERG therefore suggests the landmark analysis provides a “more reliable method of estimating the OS gain attributable to pemetrexed” without the need to extrapolate the survival curves (Section 3, page 9, LRiG, Sept 2013).

However, the PARAMOUNT study was not designed to show a survival advantage for such a small subset of patients. The Statistical Analysis Plan for the PARAMOUNT study stipulated that approximately 550 randomised patients with at least 390 death events were required to provide adequate power to show an OS advantage for pemetrexed versus placebo.

Since the landmark analysis included only 60 events from a subset of 163 patients there is a lack of statistical power in the log-rank test conducted by the ERG and thus the lack of significance cannot be directly correlated with a lack of effect and cannot provide statistically significant results to confirm their visual assessment.

Tails of the survival curves are unstable and give rise to uncertainty

The OS curves from the PARAMOUNT study provide an estimate of the underlying true population effect (which we do not know). In particular, the tail sections of the OS curves can be very unstable and the shape of the curves may change substantially as subsequent events occur due to the smaller number of patients remaining at risk of death.

Figure 3 shows the number of patients at risk together with confidence intervals (CI) for the OS estimates in each arm of the PARAMOUNT study. The width of these CIs gets wider as the number of patients at risk reduces over time, so any conclusions based on this post-hoc landmark analysis must be interpreted with due caution and without definitive conclusions.

Re-estimation of the ICER is subjective

The ERG’s landmark analysis does not depend upon extrapolation to re-estimate OS benefit. However the ERG re-estimated the ICER using a polynomial interpolation of previous ICER values which are based on extrapolated survival and costs from the lifetime economic model (Figure 5, LRiG, Sept 2013). While we appreciate that this represents a simple mathematical method for estimating intermediate points in a non-linear series, it is subjective and influenced by the choice of points on which the interpolation is drawn and the form the curve takes.

Of particular note, the ERG’s re-estimated ICER of £74,500 assumes that the re-estimated OS gain is the most reliable and is based upon plotting only three ICERs. There are other factors, beyond the OS differences, that account for the variation between these ICERs. No rationale is given for selecting only three ICERs, or for selecting these specific ICERs. Inclusion of other ICERs presented in Lilly’s submissions to this interpolation would influence the shape and slope of this curve and likely produce a different answer.

We also include below, some additional limitations of post-progression analysis, which have been used to inform the ERG's approach to OS modelling.

Limitations of post-progression survival analysis

In this appendix we respond to comments regarding post-progression survival (PPS).

The ERG state that Lilly did not address, (in the response to the second ACD), the concerns raised that the KM analysis of post-progression survival (PPS) data from PARAMOUNT showed no evidence of any patient survival benefit accruing after disease progression (Section2, page 2, LRiG, STA Second Addendum, Sept 2013). However, Lilly did in fact respond to these concerns by submitting a plausible ICER range based upon two alternative assumptions for post-trial OS benefit. One with a continuing OS benefit (as per Lilly's original basecase analysis) and another with a one-time OS benefit (paragraph 3.27 of third ACD). The latter assumption sought to address the concerns raised regarding PPS gains and gave rise to an OS gain of 3.48 months, which the ERG now believe to be plausible. During previous discussions the Committee accepted that it was not plausible that the observed OS benefit would suddenly stop on discontinuation of the trial. Thus, Lilly believe the most plausible ICER lies in the mid-range of the ICER range submitted.

While considering the plausibility of any PPS gains accrued when extrapolating survival in the economic model, it is important to highlight a number of limitations and subsequent uncertainty associated with the PPS analysis conducted during this appraisal.

The PPS analysis was conducted based upon a request from the ERG during clarification questions. This was a post-hoc analysis, and thus not pre-specified, since there is no way to design and power for PPS due to the dynamic starting point. As such the log-rank test, conducted by the ERG to demonstrate that there is no PPS benefit for pemetrexed over placebo, is not appropriate since it is not, and cannot be, adequately powered to show a statistically significant difference between arms. PPS is a non-standard endpoint which contains considerable amount of 'noise' due to the fluctuating time point at which patients become eligible for inclusion in the analysis. Moreover the final eligible patient population is different from the pre-specified ITT analysis on which other analyses and model inputs are based. PPS also considers the time period after which patients have progressed and are likely to be receiving other therapies, which may lead to bias. Finally, not all of the ITT patients had objective disease progression (PD) at the final datalock of the PARAMOUNT study.

Accordingly, the PPS analysis should be interpreted with due caution and specifically the log-rank test conducted by the ERG should not be used to support the ERG's assertion that there is no PPS benefit for pemetrexed.

References:

1. 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.

2. Liverpool Reviews and Implementation Group (LRiG): Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer. Addendum. 27th September 2013.