Appendix 1: Application of the supplementary advice on 'End of life' in the context of the size of the cumulative patient population eligible for pemetrexed

- We acknowledge the basic principles of the 'End of Life' criteria – helping patients gain access to life-extending treatments and rewarding manufacturers of innovative treatments that are indicated for conditions with small patient populations. However, the Committee's approach in determining the population size for the purposes of the ACD is not fair and does not reflect the proposed use of pemetrexed.

- The estimation of the cumulative licensed population is fairly clear when the licensed populations for each indication are mutually exclusive, for instance, NSCLC and mesothelioma. However, for indications which cover different settings of same disease but at different points in the treatment pathway (as in different settings of NSCLC) is not straightforward.

- By double-counting patients receiving continuation and switch maintenance, as documented in paragraphs 4.23 and 4.24, the Committee has applied the 'End of life' advice is inconsistent with that applied in other appraisals.

Estimated pemetrexed-eligible population as calculated by Lilly

Table 1 presents Lilly's position on the estimated population eligible for pemetrexed as documented in the ACD, while Figure 1 depicts Lilly's calculation of patients eligible for pemetrexed across all licensed indications. For comparison purposes, patient numbers as calculated in the ACD are also presented in Figure 2. Figure 3 shows the two main pools of patients who are eligible for pemetrexed treatment in NSCLC.

Table 2 provides a detailed explanation of the calculation of patient numbers.

Total estimated population eligible for pemetrexed across all licensed indications

- The total eligible population that the Committee should consider is **n=6184** (n=1606 for mesothelioma + n= 4555 for PS 0-1 first-line NSCLC + n=23 for PS 2 second-line NSCLC).

- Even applying the most conservative approach and double counting the continuation maintenance population (n=588), the patient population eligible for pemetrexed across all licensed indications is **n=6772**.

- Inclusion of switch maintenance patients is inappropriate as these patients by the nature of the indication must have <u>not</u> received pemetrexed first-line to be eligible for maintenance.

- Therefore, **the total population of patients who may receive pemetrexed falls beneath the 7000 threshold**, which means that pemetrexed should qualify for 'End of Life' consideration in terms of the small population criterion.

Table 1. Lilly's position on estimated pemetrexed-eligible population as document in the ACD

Indication / setting	Estimated eligible population in ACD / ACD paragraph	Numerical value accepted by Lilly Yes/No	Double-counted in ACD Yes/No	Rationale for alternative Lilly estimate
Mesothelioma	1606 (Para 4.25)	Yes	N/A	N/A
First-line NSCLC, Non-squamous patients with stage IIIB/IV and PS 0-1	4555 (Para 4.22)	Yes	N/A	N/A
Continuation maintenance NSCLC	535, updated to 588 based on NLCA 2012 (Para 4.23)	Yes	Yes	We do not believe continuation maintenance should be included as it is essentially an extension of first-line treatment to progression in the same patient.
Switch maintenance	1100 – 535= 565 (Para 4.23)	No - N/A	Yes	Inappropriate to include these patients as they have not received pemetrexed in the first-line setting.
Second-line Non-squamous NSCLC, PS 2 only	1500 (Para 4.24)	No	N/A	We estimate this number to be n= 23. The number in the ACD is an overestimate based on a misinterpretation of the Clinical Specialists' comments "one third of PS 2 patients would receive chemotherapy". Comment was in relation to 1st-line chemo, not 2nd-line as inferred by the Committee.

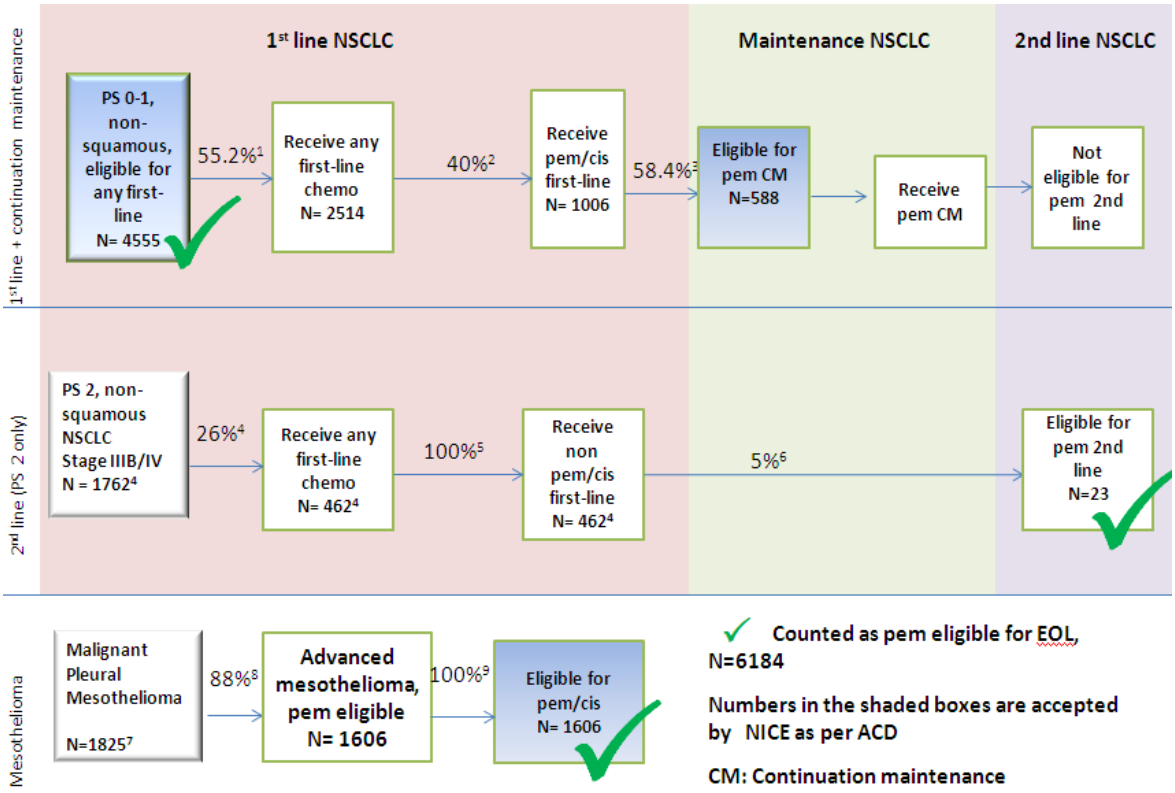
Since the population size is a crucial criterion for consideration under the EOL supplementary advice, we would like to request that Figure 1 be shown to Committee members at the second AC meeting to facilitate understanding and inform the Committee's discussions around these numbers (a powerpoint presentation with the figure is attached).

Table 2. Detailed explanation of calculations for estimated patient numbers for NSCLC settings

Sr no.	Indication /setting	Explanation of calculations of estimated pemetrexed-eligible population
1.	First-line NSCLC, PS 0-1	• As mentioned in the ACD, we have assumed that **all** patients with non-squamous stage IIIB/IV NSCLC with PS 0-1 (n=4555) are potentially eligible for first-line treatment with pemetrexed/cisplatin. • These 4555 patients represent the maximum population of PS 0-1 NSCLC patients who can ever be eligible for pemetrexed therapy - irrespective of the particular regime or place in the treatment pathway. • In actual clinical practice, only 55.2% of these (n=2514) receive first-line treatment (NLCA audit report 2012), of which 40% receive pemetrexed/cisplatin (N=1006) (GfK Market data Q4 2012).
2.	Continuation maintenance treatment of NSCLC	• Paragraph 4.23 of the ACD states "*The Committee noted that the manufacturer estimated the population eligible for "continuation maintenance" to be 535".* The Committee accepted this figure (based on the NLCA 2011 audit report) for the purposes of its calculations. • In the PARAMOUNT study, the pivotal trial for pemetrexed in continuation maintenance treatment (Paz-Ares et al 2012), 58.4% of patients receiving pemetrexed first-line were eligible to continue on pemetrexed monotherapy. We suggest amending the figure of the N=535 in the ACD paragraph 4.23 based on the data from the NLCA 2012 audit report to obtain an estimated N=588 patients (i.e, 58.4% of the n=1006 patients who actually receive pemetrexed/cisplatin first-line).
3.	Switch maintenance treatment of NSCLC	• Paragraph 4.23 of the ACD states 'The committee noted that the manufacturer estimated the population eligible for 'continuation maintenance to be 535. "*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. Thus approximately 1100 patients would be eligible to receive pemetrexed maintenance treatment*.' The Committee have accepted that n=535 patients are eligible for continuation maintenance, which leaves 1100 minus 535 = 565 patients eligible to receive pemetrexed switch maintenance. There is no basis for this number other than the Committee's perception that the number of patients receiving switch and continuation maintenance are equal.
4.	Second-line treatment of NSCLC, PS 2 patients	• PS 2 patients are not fit enough to receive pemetrexed in combination with cisplatin as first-line treatment (and therefore, as maintenance treatment), however pemetrexed may be prescribed as monotherapy in the second-line setting. • In paragraph 4.24, the ACD refers to advice received from the clinical specialists that there were approximately equal numbers of NSCLC patients presenting with a performance status of 2 and 0-1 (i.e. 4555 in each group), that approximately one third of patients of performance status 2 would receive chemotherapy and concludes "*the Committee therefore considered that the second-line population eligible for pemetrexed would be one third of 4555, that is, approximately 1500 patients*". • However, the Committee's conclusion relates to the proportion of patients with PS 2 potentially eligible for *first-line chemotherapy* and not to eligibility

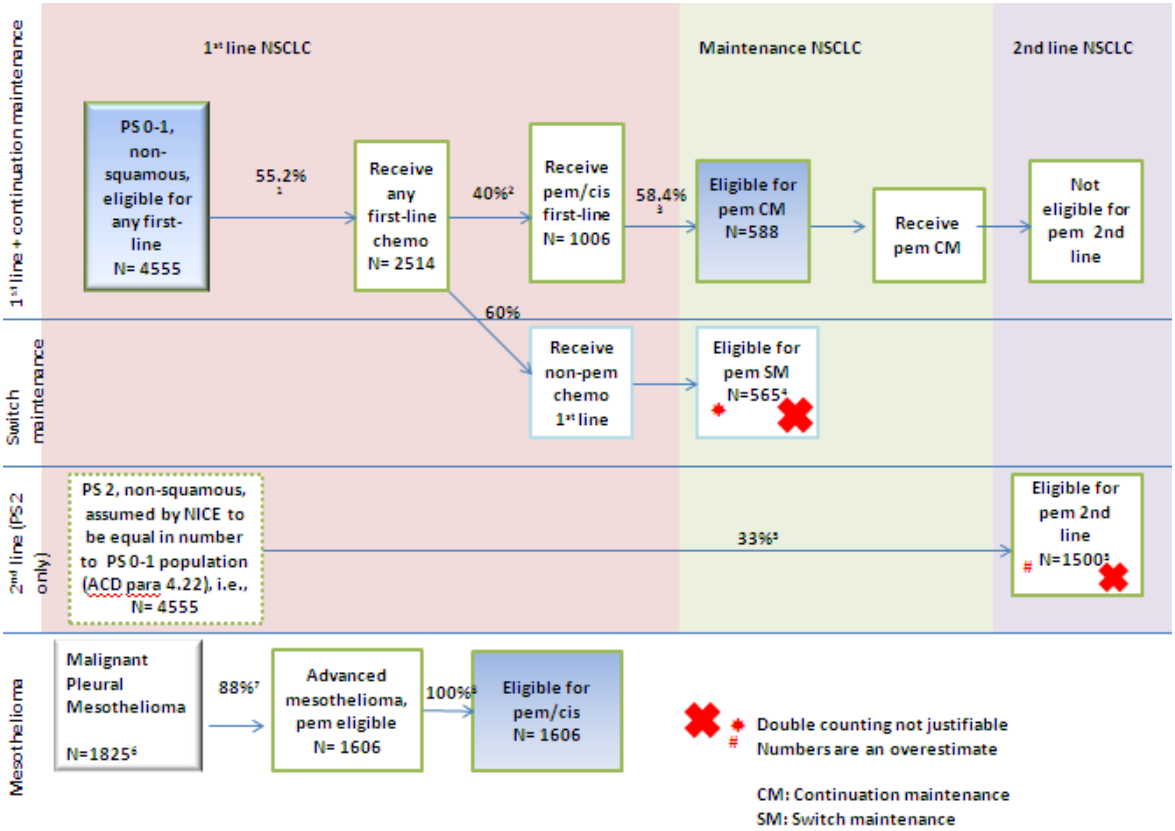
		for second-line treatment with pemetrexed. In order to estimate the eligible second-line population, we first have to estimate the number of patients receiving first-line chemotherapy. • Data from the NLCA 2011 cohort shows that there are 1762 patients with non-squamous stage IIIB/IV NSCLC with PS 2 (Personal communication, Dr M. Peake, 2013). This figure suggests that the Committee's figure of 4555 patients presenting with a performance status of 2, represents an over-estimate. Of the 1762 PS 2 patients identified in the 2011 NLCA, 462 received first-line chemotherapy. Since only 5% of patients receiving first-line chemotherapy are estimated to be eligible for 2nd-line (Personal communication, Dr J. Lester, March 2013), only 23 are estimated to be eligible for second-line treatment, based on clinical expert opinion.

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



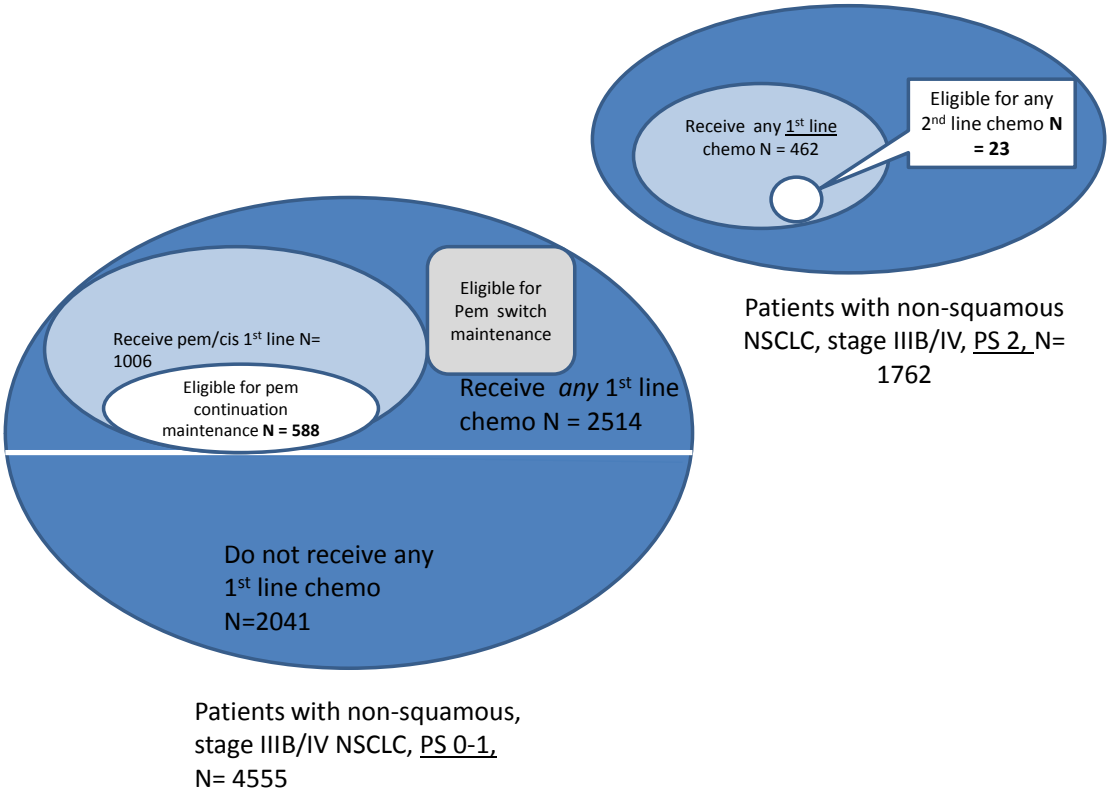
CM: Continuation maintenance; [1]Percentage of PS 0-1 Stage IIIB or IV NSCLC pts having chemotherapy, Page 39, NLCA Audit report 2012; [2] Pem/cis Share of market, GfK Market data Q4 2012; [3] Percentage patients eligible for pemetrexed continuation maintenance from the PARAMOUNT trial (Paz-Ares et al 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

Figure 2. Patients eligible for pemetrexed across all licensed indications - as calculated in the ACD



CM: Continuation maintenance; SM: Switch 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] Pemetrexed ACD paragraph 4.23 (1100 – 535 = 565); [5] Pemetrexed ACD paragraph 4.24 (a third of 4555 = approx. 1500 pts); [6] NLCA Audit report 2012 page 8; [7] Pemetrexed ACD paragraph 4.25 ; [8] Assumption.

Figure 3. Patients eligible for pemetrexed treatment in the NSCLC



Note: Patients eligible for pemetrexed treatment in any NSCLC setting originate from two main pools of patients (see Figure 1). Any patients who receive pemetrexed in any setting of NSCLC have to belong to either of these two pools of patients. The first pool consists of N= 4,555 patients with non-squamous stage IIIB/IV NSCLC and PS 0-1 (NLCA 2012). The second is a separate pool of N=462 patients with non-squamous stage IIIB/IV NSCLC and PS 2 (Personal communication, Dr M. Peake. 2011 cohort. March 2013).

References:

1. 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.
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. 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. Lilly data on file. GfK market research Q4 2012
5. National collaborating Centre for Cancer. The diagnosis and treatment of lung cancer (update). NICE Clinical Guideline 121; Wales: 2011. http://www.nice.org.uk/nicemedia/live/13465/54199/54199.pdf
6. 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.

7. 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.