NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Pemetrexed for the treatment of relapsed non-small cell lung cancer

Response to consultee and commentator comments on the Appraisal Consultation Document (ACD)

Organisation	Section	Comment	Response
The Roy Castle Lung Cancer Foundation	Has all of the relevant evidence been taken into account	The Foundation is not in the position of being able to carry out systematic reviews of the scientific literature and is unable to make comment on this.	Comment noted
The Roy Castle Lung Cancer Foundation	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	The obvious benefits of this drug over Docetaxel are in the side effect profile. For Pemetrexed, there is less potentially fatal neutropenia and considerably less alopecia. Both of these are of considerable importance in this group of patients (especially hair loss in women), who have such a short prognosis.	The Committee acknowledged that hair loss can be distressing, but concluded that the higher rate of alopecia would not normally preclude consideration of a particular chemotherapy regimen. The Committee noted the differences in the toxicity profiles of the two drugs when formulating its recommendations.

The Roy Castle Lung Cancer Foundation	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	There would, of course, be a small group of patients who have had an allergic reaction to Docetaxel, for whom there is currently no further NICE approved active anti-cancer agents. Pemetrexed would be important in this small group and without NICE Guidance to support this, past experience shows that it would not otherwise be made available in the NHS.	The Committee considered the role of pemetrexed in the treatment of patients who have had an allergic reaction to docetaxel. The Committee heard from the clinical specialists that some patients experience mild allergic reactions to docetaxel (such as rash or nausea). In these circumstances it is usual to treat the reaction rather than discontinue treatment and therefore did not consider it appropriate to modify the general guidance on use of pemetrexed therapy on this basis.
The Roy Castle Lung Cancer Foundation	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	Cost effectiveness – The Foundation does not have access to health economic specialists. However, the massive discrepancy between the cost figures tabled by the manufacturer and those calculated by the report evaluators, causes considerable concern. We are aware that very small deviations in assumptions can skew calculation results massively. As a patient group, we would be concerned if the Appraisal Committee decision were made on this basis alone.	Comment noted
The Roy Castle	Are the	Impact on the NHS – The number of patients who would be suitable for	The commonality or rarity of

Lung Cancer Foundation	summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	this treatment would be relatively small. These patients would be on this treatment for a very short period (weeks to months), Thus, the overall cost to the NHS of recommending this drug, would be very small. The benefit to this patient population, of having an additional treatment option, would be great. This does not appear to be reflected in the ACD.	people eligible for treatment is not considered by the Committee.
Castle Lung Cancer Foundation	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	We would like to bring to the Appraisal Committee's attention, the conclusions of the attached, recently published paper [Bedano et al, Salvage Therapy in Patients with Advanced nsclc. Journal of Thoracic Oncology 2006,1:582 – 587]. This review of the role of second line chemotherapy in the management of advanced nsclc concludes that "For smokers who have benefited from first-line chemotherapy and are maintaining a PS 0 and 1, a trial of Pemetrexed is reasonable". This differs somewhat from the conclusion reached in the ACD.	Comment noted
Castle Lung Cancer Foundation	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	As active treatment options are so limited in advanced nsclc and as outcomes remain so poor, the availability of new choices, offer a glimmer of 'hope' for patients. We do not consider that this ACD reflects the desperate nature of this patient population. Pemetrexed offers new hope and an alternative for this desperate group of patients. We urge the Appraisal Committee to take this into account.	The Committee acknowledged that there are currently few treatment options available for people with advanced NSCLC. However, after careful review of all the evidence, it concluded that pemetrexed could not be recommended.

Network Pharmacists	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	There are no additional comments which the group would like to offer in respect of this appraisal and the Pharmacists agree with the preliminary recommendations; based on the evidence presented in the consultation document.	Comment noted.
Cancerbackup	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	Cancerbackup welcomes the opportunity to contribute to the appraisal of pemetrexed (Alimta) for the treatment of non-small-cell lung cancer (NSCLC). As the leading specialist provider of independent information on all types of cancer, Cancerbackup has regular contact with people living with NSCLC and those caring for them. Cancerbackup receives over 2,800 telephone enquiries about lung cancer each year and almost 94,000 visitors to our website pages on lung cancer. Cancerbackup believes that everyone with cancer should be offered the most effective and appropriate treatment for them, based on the available evidence and the patient's own wishes and preferences. We believe that: • Patients should have access to the most effective treatments appropriate to them as individuals; • Patients should be able to choose – in partnership with their oncologist – the treatment that is likely to suit them best in terms of relative benefits and side-effects; The impact of treatments on patient's quality of life, as well as length of	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. This included information on length and quality of life. See Guide to the Methods of Technology Appraisal section 5.3.4 (Available from URL http://www.nice.org.uk/page.aspx?o=201974).

		life, should be given full consideration by the Appraisal Committee.	
Cancerbackup	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	Around 37,127 people are diagnosed with lung cancer in the UK each year[1]. Lung cancer is a devastating disease with poor survival expectations; just 6% of people with lung cancer survive for five years after diagnosis[2]. Pemetrexed offers new hope for people with lung cancer, who would benefit greatly from improved quality of life in the last few months of their lives. Toxicity with pemetrexed is considered to be mild. For patients with very few treatment options available to them, this is a hugely important consideration and can enable people with lung cancer to carry out every day activities and lead a more active life.	The Committee considered evidence from NSCLC patient groups and took this into account when making its recommendations.
Cancerbackup	whether you consider that all of the relevant evidence has been taken into account	Cancerbackup is disappointed that the ACD does not recommend the use of pemetrexed for the treatment of non-small-cell lung cancer and urges the Appraisal Committee to reconsider this decision, and to approve the technology for use in the NHS for the following reasons 1. Pemetrexed can improve patients' quality of life The clinicians who advise Cancerbackup's work tell us that pemetrexed is considered to be better tolerated than comparable treatments. A phase II trial of pemetrexed in patients with stage II or IV NSCLC gave 59 patients a median of four cycles of pemetrexed[3]. The trial showed that while grade 3 or 4 neutropenia (an abnormally low number of immature white blood cells, which ordinarily help fight infection) was seen in 25	The Committee decision was based on a detailed review of the evidence, and included consideration of the side effects associated with pemetrexed and docetaxel.

[1] CancerStats Report, Cancer Research UK
[2] Ibid.
[3] S J Clarke, R Abratt, L Goedhals, M J Boyer, M J Millward, S P Ackland, 'Phase II trial of pemetrexed disodium (Alimta) in chemotherapy-naïve patients with advanced non-small-cell lung cancer', Annals of Oncology 13: 737-41, 2002

		patients (42%), only two patients (3%) developed grade 3 infection.	
Cancerbackup	whether you consider that all of the relevant evidence has been taken into account	A phase II study looked at 79 patients with NSCLC who had progressive disease within 3 months after first-line chemotherapy or progression while being treated with first-line chemotherapy[4]. Toxicity was found to be mild, with grade 4 granulocytpenia (a low level of granular white blood cells, which ordinarily help fight infection) seen in 15 patients (19%), and grade 4 thrombocytopenia (a low level of platelets, which help the blood to clot) in four patients (5%). Clinical toxicity occurred infrequently with grade 3 rash, infection, nausea, vomiting, fatigue and pulmonary toxicity (lung damage – either short term or permanent) in four (1.6%), one (0.4%), one (0.4%), two (0.8%), four (1.6%) and one (0.4%) cycles, respectively. These are important considerations for patients who, with stage III or IV NSCLC, have limited treatment options which can both improve survival outcomes and improve their quality of life.	The Committee decision was based on a detailed review of the evidence, and included consideration of the side effects associated with pemetrexed.
Cancerbackup	whether you consider that all of the relevant evidence has been taken into account.	2. Pemetrexed can lengthen survival for people with NSCLC A controlled, unblinded trial of people with locally advanced or metastatic NSCLC who had received prior chemotherapy randomised 571 patients to receive either pemetrexed or docetaxel. The median survival times were 8.3 months in the pemetrexed arm and 7.9 months in the docetaxel arm[5]. Pemetrexed offers an important additional treatment option, with the ability to lengthen for people with NSCLC whose treatment options are few.	The Committee concluded that pemetrexed does not offer improved survival compared to docetaxel (see FAD section 4.2).

[4] E F Smit, K Mattson, J von Pawel, C Manegold, S Clarke and P E Postmus, 'Alimta (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer: a phase II study', Annals of Oncology 14: 455-460, 2003

[5] Matin H cohen, John R Johnson, Yong-Cheng Wang, Rajeshwari Sridhara, Richard Pazdur, 'FDA Drug Approval Summary: Pemetrexed for Injection (Alimta) for the Treatment of Non-Small Cell Lung Cancer', The Oncologist 2005; 10: 363-368

Royal College of Nursing	General Point:	At the National Cancer Research Institute (NCRI) meeting in October 2006, research into Lung Cancer was highlighted as a priority but one may ask what the point of conducting the research is, if NICE would not fund the new drugs? This could stifle investment in future research and we can not overemphasis the importance of funding these treatments for patients' benefit and quality of life.	Decisions are made on the basis of clinical and cost effectiveness. This included consideration of the effect of treatment on patients' quality of life.
Royal College of Nursing	whether you consider that all of the relevant evidence has been taken into account	NICE appears to have dismissed the advantages of Alimta and failed to mention what is the most important benefit of this drug to patients, which is the lack of myelosuppression. This is a critical advantage over docetaxel for those patients who have previously demonstrated myelosuppression and this must have a significant cost-saving by keeping patients out of hospital.	The Committee decision was based on a detailed review of the clinical and cost-effectiveness evidence which took into account the costs of hospitalisation and treatment for neutropenia.
Royal College of Nursing	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	From a nursing perspective the toxicity profile of Alimta needs to be stressed as an important advantage in terms of patient benefit. Particularly in terms of alopecia which in some instances is a significant cause of concern for patients, although may not necessarily influence the patient's choice of docetaxel versus no treatment (for patients this is not a choice as they wish to have treatment) but does have a significant effect on quality of life issues. We would therefore, ask that patients who wish to avoid alopecia should be given the option/choice of avoiding this by having Alimta.	Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 5) The Committee acknowledged that hair loss can be distressing, but concluded that the higher rate of alopecia

			would not normally preclude consideration of a particular chemotherapy regimen
Royal College of Nursing	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	The toxicity profile of docetaxel also means that patients are more likely to require hospital admission, further blood tests and delays in treatment than with Alimta	The Committee decision was based on a detailed review of the clinical and cost-effectiveness evidence which took into account the costs associated with the management of adverse events.
Royal College of Physicians (RCP)	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	Around 35% of patients with NSCLC in the UK currently receive 1st Line chemotherapy. The proportion of these who go on to receive second line chemotherapy is not well researched but expert opinion from the National Lead Clinician for lung cancer and from the National Lung Cancer Audit programme suggests that no more than 20% of this 35% go on to receive 2nd line chemotherapy (i.e. 7% overall). This very low proportion is largely a result of the fact that many oncologists feel the toxicity and overall poor tolerability of docetaxel in this group of patients at this stage of their disease is too high to outweigh the relatively low response rates and modest survival gain. There is a very high rate of hospitalisation for febrile neutropaenia with docetaxel (well over 10% in most centres) and alopecia is common – another very distressing side effect for patients with only a few months to live.	The Committee considered the possible role of pemetrexed for people for whom docetaxel therapy is unsuitable. However, after careful consideration of all the evidence, the Committee concluded that pemetrexed could not be recommended for these people (see FAD sections 4.8-4.12)

		Good, less toxic agents are urgently required in this setting. Having less toxic alternatives available would result in a higher proportion of patients being eligible to receive second line therapy which would be likely to result in a modest, but significant improvement in survival and quality of life in this particular group of patients for whom there are currently limited options. Pemetrexed is such an alternative and as such needs serious consideration	
RCP	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	We believe that NICE has failed to recognise the significance of the differences of the toxicity profiles of docetaxel in comparison with pemetrexed, particularly as they affect this specific patient group.	The Committee were aware of the differences in toxicity profiles of docetaxel in comparison with pemetrexed (see FAD section 4.3).
RCP	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence	We also believe that NICE have underestimated the costs of the growth factor support (G-CSF) required for the safe administration of docetaxel by underestimating the proportion of patients who should be receiving it. ASCO guidelines recommend the routine use of G-CSF in the management of patients with febrile neutropenia and also recommend the prophylactic use of G-CSF in patient groups with a high likelihood of this adverse event. Pemetrexed has substantially less haematological toxicity than docetaxel and therefore G-CSF would be rarely required. We	The Committee acknowledged there was uncertainty about the extent of G-CSF usage in clinical practice in the UK. The Committee considered that if G-CSF were used in the proportion the experts suggested, inclusion of this

	and the views on the impact to the NHS appropriate	believe that this lower requirement for the use of G-CSF should significantly reduce the ICER for pemetrexed in comparison with docetaxel	factor would not lead to a substantial improvement in the cost effectiveness of pemetrexed compared to docetaxel.
RCP	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	It is not clear to us how the ERG arrived at some of their cost estimates, especially the cost per QALY of £458,333 – it is vital that these crucial analyses are entirely transparent and consistent. We are not convinced that the analyses of the ERG meet either of these requirements	Please see the ERG report (Section 4.3).
RCP	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	We would also like to point out that the ERG used an average Body Surface Area of 1.83m^2 to calculate the average cost of a course of pemetrexed treatment - this in our experience is significantly higher than patients in this disease group in the UK. We estimate it to be between 1.65 and 1.7 – a difference that would significantly reduce the ICER for pemetrexed.	The Committee acknowledged that BSA would vary between patients and concluded that the mean BSA could be lower than the ERG estimate particularly in patients with relapsed NSCLC. The Committee considered the manufacturer's estimate (1.7) to be appropriate, but concluded that this factor would not substantially change the ICER.

RCP	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	Apart from the generality of patients potentially eligible for second line chemotherapy, there are at least two specific sub-groups of patients in whom the availability of an effective alternative to docetaxel as second line treatment is urgently required; these are: o Patients allergic to docetaxel Patients who received docetaxel first line and who have relapsed There is also a larger group of patients, as implied in the opening paragraph, who are currently considered unfit for docetaxel who could benefit from a less toxic agent. We would therefore urge NICE to reconsider the limited options available to patients and oncologists in this common clinical situation and the potential benefits to survival (if modest), quality of life and lower toxicity profile of pemetrexed. We urgently need alternatives to docetaxel for a limited number of patients.	The Committee considered the role of pemetrexed in the treatment of patients who are unsuitable for docetaxel. The Committee concluded that pemetrexed would not be a cost-effective use of NHS resources and could not be recommended. (see FAD 4.8 to 4.12)
British Thoracic Society	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and the views on the impact to the NHS appropriate	The Appraisal Committee assessment of the cost of the use of pemetrexed, suggests that it is not a cost effective treatment compared to docetaxel as second line treatment for advanced lung cancer, however many clinicians find that neutropaenia is a problem with docetaxel as second-line treatment and leads to significant rates of hospitalization for febrile neutropaenia. Others are using growth factors routinely to prevent these complications. If the cost of these were to be included in the calculation, the cost of pemetrexed would be more favourable.	The Committee decision was based on a detailed review of the clinical and cost-effectiveness evidence which took into account the costs of hospitalisation and treatment for neutropenia. The Committee acknowledged there was uncertainty about the extent of G-CSF usage in clinical practice in the UK. The Committee considered that if

			G-CSF were used in the proportion the experts suggested, inclusion of this factor would not lead to a substantial improvement in the cost effectiveness of pemetrexed compared to docetaxel.
British Thoracic Society	whether you consider that all of the relevant evidence has been taken into account	The numbers of patients with lung cancer suitable for second line treatment is small, less than 10% of all patients with non-small cell lung cancer.	The commonness or rarity of people eligible for treatment is not considered by the Committee.
British Thoracic Society	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	If pemetrexed and erlotinib are both rejected by NICE, as not cost effective treatments, there will be nothing to offer patients who could benefit from alternative second or third line treatment, and the sub-group of patients that all clinicians have seen with exceptional responses will be deprived of treatment.	The Committee noted the limited treatment options available to patients. The Institute's remit is to make recommendations after an assessment of the costs and benefits of treatment.
British Thoracic Society	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance?	Were the Committee to decide that, at this time following submission of the proposed request for further evidence from the manufacturer's, they could not recommend the use of erlotinib in patients with advanced non-small cell lung cancer, given the rapidity with which data on sub-group analysis and selection of patients through receptor status etc is being accrued, I do not believe that further review could be left for the standard period of three years.	Comment on the NICE appraisal of erlotinib noted.
Sanofi-aventis	Are these provisional recommendations sound and a	sanofi-aventis agrees with the conclusions and recommendations within this ACD. The head-to-head registrational trial comparing pemetrexed vs. Taxotere® (docetaxel) in second line NSCLC found neither a survival benefit or a quality of life benefit for patients (Hanna et al. 2004. Journal	Comment noted.

	suitable basis for preparing NHS guidance?	of Clinical Oncology, 22:1589-1587). Given the additional purchase cost of pemetrexed, and the absence of any patient benefit (vs. docetaxel), the cost effectiveness calculations suggest the availability of pemetrexed on the NHS in England and Wales does not represent an effective use of already stretched drug purchasing budgets.	
Department of Health (DH)	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	Around 35% of patients with NSCLC in the UK receive 1st Line chemotherapy. The proportion of those who go on to receive second line chemotherapy is not well researched but, based on experience, our clinical colleagues would estimate that not more than 20% of this 35% go on to receive 2nd line chemotherapy (i.e. 7% overall). This very low proportion is largely a result of the fact that many oncologists feel the toxicity and overall poor tolerability of docetaxel in this group of patients at this stage of their disease is too high to outweigh the relatively low response rates and modest survival gain. There is a very high rate of hospitalisation for febrile neutropaenia with docetaxel (well over 10% in our experience) and alopecia is common. Good, less toxic agents are urgently required in this setting. Having less toxic alternatives available would result in a higher proportion of patients receiving second line therapy which clinical colleagues feel would be likely to result in a modest, but significant improvement in survival and quality of life in this particular group of patients for whom there are currently limited options	The commonality or rarity of people eligible for treatment is not considered by the Committee. The committee decision was based on a detailed review of the clinical and cost-effectiveness evidence which took into account the costs of hospitalisation and treatment for neutropenia. It also acknowledged that hair loss can be distressing, but concluded that the higher rate of alopecia would not normally preclude consideration of a particular chemotherapy regimen.

DH	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	Apart from the generality of patients potentially eligible for second line chemotherapy, clinical colleagues advise that there are at least two specific sub-groups of patients in whom the availability of an effective alternative to docetaxel as second line treatment is urgently required; these are: • Patients allergic to Docetaxol • Patients who received Docetaxol first line and who have relapsed There is also a larger group of patients who are currently considered unfit for docetaxel who could benefit from a less toxic agent. We would be grateful if NICE could reconsider the limited options available to patients and oncologists in this common clinical situation and the potential benefits to survival (if modest), quality of life and lower toxicity profile of Pemetrexed. Alternatives to docetaxel are urgently needed for a limited number of patients	The Committee considered the role of pemetrexed in the treatment of patients who have had an allergic reaction to docetaxel. (See FAD Section 4.8) It also considered the possible role of pemetrexed for people for whom docetaxel therapy is unsuitable. However, after careful consideration of all the evidence, the Committee concluded that pemetrexed should not be recommended for these people (see FAD sections 4.8-4.12)
DH	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and	In our opinion, we feel the guidance may have mis-judged the significance of the differences of the toxicity profiles of docetaxel vs. pemetrexed, particularly as they affect this specific patient group. We also feel the guidance may have underestimated the costs of the growth factor support (GSF) with docetaxel by possibly underestimating the proportion of patients who should be receiving it - treatment which ASCO guidelines recommend routinely in the management of febrile neutropaenia and even prophylactically in patient groups with a high likelihood of this adverse event. We feel that the lower requirement for the use of GSF with pemetrexed alone would make a significant impact on the ICER	The Committee carefully considered the different toxicity profiles of the two treatments. It concluded that pemetrexed would not be a cost effective use of NHS resources. The Committee acknowledged there was uncertainty about the extent of G-CSF usage in clinical practice in the UK. The Committee considered that if

	implications for the NHS are appropriate		G-CSF were used in the proportion the experts suggested, inclusion of this factor would not lead to a substantial improvement in the cost effectiveness of pemetrexed compared to docetaxel.
DH	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The guidance does not make it clear how the ERG arrived at some of their cost estimates, especially the cost per QALY of £458,333 – would it be possible to set out these analyses more clearly?	Details of how the methods and results of the ERG's illustrative analysis are provided in the ERG report (available from http://www.nice.org.uk/page.aspx?o=383541
DH	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence	In addition, the ERG used an average Body Surface Area of 1.83m^2 to calculate the average cost of a course of pemetrexed treatment – in the experience of clinical colleagues, this is significantly higher than patients in this disease group in the UK. They estimate it to be between 1.65 and 1.7 – a difference that would significantly reduce the cost per QALY of pemetrexed.	The Committee acknowledged that BSA would vary between patients and concluded that the mean BSA could be lower than the ERG estimate particularly in patients with relapsed NSCLC. The

	and that the preliminary views on the resource impact and implications for the NHS are appropriate		Committee considered the manufacturer's estimate (1.7) to be appropriate, but concluded that this factor would not substantially change the ICER.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	In the Lilly submission, pemetrexed was clearly positioned, not as a substitute for docetaxel as standard of care in second-line NSCLC, but as an alternative option to docetaxel in the following circumstances, where Best Supportive Care (BSC) would be conventional therapy: 1) if the patient has received a taxane (docetaxel or paclitaxel) as their first-line treatment and cannot be re-exposed to docetaxel (approximately 20% of first-line NSCLC patients, UK market research data) 2) if the patient is allergic to or unable to tolerate docetaxel and yet is suitable for active chemotherapy; and/or 3) if the physician and/or patient has significant concerns regarding toxicity associated with docetaxel. It is for these reasons, and, notably, at the request of NICE when defining the decision problem, that Lilly included an unadjusted (pooled) and adjusted (anchored using hazard ratios) indirect comparison to BSC in the submission. The Lilly submission on pemetrexed presented an economic model to the ERG that allowed them to perform either adjusted or unadjusted indirect comparisons, in keeping with the agreed scope of the NICE Decision Problem; that being to compare pemetrexed against docetaxel, erlotinib and best supportive care.	The decision problem submitted by the manufacturer does not give preference to the comparison versus BSC over that versus docetaxel. This is exemplified in their summary of the decision problem: 'The remit of this appraisal is to assess the clinical and cost effectiveness of pemetrexed compared to current standards of care in second-line advanced non-small cell lung cancer (NSCLC). Various treatment scenarios including other licensed therapies in second-line NSCLC (docetaxel and erlotinib) will be explored as will Best Supportive Care (BSC). The aim of the economic evaluation is to determine which therapy options provide the greatest

			benefit and cost-effectiveness.' [page 11 of manufacturer submission] The Committee considered the possible role of pemetrexed for people for whom docetaxel therapy is unsuitable. However, after careful consideration of all the evidence, the Committee concluded that pemetrexed should not be recommended for these people (see FAD sections 4.8-4.12). The Committee carefully considered both indirect comparisons submitted by the manufacturer.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and	There is a strong clinical case to support the use of pemetrexed: Pemetrexed is the first single-agent therapy that has been licensed for second-line therapy in patients with advanced NSCLC based on a Phase III RCT (JMEI) that used docetaxel as a comparator. The trial results are based on 541 patients (265 patients on the pemetrexed arm, and 276 patients on docetaxel). In this study, pemetrexed and docetaxel achieve comparable survival and marketing authorisation was given on this basis in 79 countries worldwide. Docetaxel is recommended by NICE and recognised by regulators as providing significant survival benefit over BSC; therefore, it can be assumed pemetrexed also provides benefit over BSC.	Comment noted.

	implications for the NHS are appropriate		
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	Febrile neutropenia is associated with a mortality of 9.5% in hospitalised cases (Kuderer et al, 2006). In the JMEI trial 1 in 8 patients who receive docetaxel, compared to 1 in 55 patients who receive pemetrexed, experienced febrile neutropenia. This is a significant reduction in risk for patients with advanced cancer treated with pemetrexed. Significantly fewer patients treated with pemetrexed in the JMEI trial were hospitalised due to febrile neutropenia than those treated with docetaxel (2% vs 13%); likewise, significantly fewer patients treated with pemetrexed- required G-CSF support (3% vs 19%).	The Committee were aware of the differences in toxicity profiles of docetaxel in comparison with pemetrexed (see FAD section 3.3).

Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	There are additional severe and life-threatening toxicities associated with docetaxel which require hospitalisation, such as grade 3/4 diarrhoea and vomiting. It is unfortunate that the Appraisal Consultation Document (ACD) and ERG documents undermine the significance of patients to experiencing severe treatment related side-effects associated with docetaxel as these have a significant impact on the well being of the NSCLC patient.	The Committee considered evidence from NSCLC patient experts and the evidence from the clinical trials regarding the differences in toxicity profiles of the two treatments.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	Pemetrexed costs £640-800 per cycle more than docetaxel for a mean of 4 cycles, a total cost increase of around £3000 per treated patient. The cost of managing one episode of febrile neutropenia is quoted as £3582 by both Lilly in the current submission, Roche in the erlotinib submission and Aventis in the original submission for docetaxel.	Comment noted.

Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The ERG has over-emphasised the comparison of pemetrexed to docetaxel, has rejected the unadjusted economic comparison and yet failed to utilise the adjusted indirect comparison that was provided. It is of note that the economic case for erlotinib described in the Roche submission also employed an unadjusted method of indirect comparison alone to compare erlotinib to docetaxel and yet the ERG has not rejected this analysis.	The committee carefully considered the base case analysis based on an unadjusted indirect comparison and the sensitivity analysis based on adjusted indirect comparison of pooled hazard rates from several trials. It also carefully considered the comparison with docetaxel and the comparison with BSC. The Committee considered both indirect comparisons inappropriate given the inconsistency of the findings in relation to the direct randomised comparison between pemetrexed and docetaxel in the JMEI trial.
Eli Lilly	Are these provisional recommendations sound and a suitable basis for preparing NHS guidance	The presentation of extreme cost per QALY results by the ERG (particularly in a situation of comparable efficacy where cost per QALY estimates tend to be unstable and sensitive to very small changes in outcome) is not conducive to evidence-based pragmatic decision-making in the NHS, does not support the balanced appraisal of clinical benefit by the appraisal committee and finally, fails to adequately represent the patients' or physicians' perspective in treating a terminal disease where the palliation is the key aim of treatment.	Comment noted

Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The mean number of cycles used by the ERG to estimate the treatment cost of pemetrexed in the ACD was 5 (page 3). However the mean number of cycles administered in the JMEI trial was 3.9 for docetaxel and 4.4 for pemetrexed (no significant difference), the median was 4 cycles for each arm. The model provided by Lilly demonstrated an average use of 3 cycles per patient, based upon treatment until progression or discontinuation. This reflects expected UK practice and, as such, is supported on page 20 of the ERG report. The pivotal impact of the duration of therapy on the cost per QALY is highlighted by the ERG in their report.	The mean number of cycles in the ERG analysis was 4.3. The Committee considered that the estimates used in the ERG analysis were the most appropriate as they were based on the same trial as the effectiveness data.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.	The ERG has assigned a body surface area (BSA) that is too high for advanced lung cancer patients. The average body surface area used by Lilly was $1.7m^2$. This was based on a large naturalistic study of first-line NSCLC patients in the UK (n=197) which showed the average BSA was $1.80m^2$ (Bischoff 2005). It is perfectly legitimate to assume that patients receiving second-line treatment for NSCLC are thinner than those at first-line, as the patient loses weight over the course of the illness. This assumption was endorsed by UK clinical experts and pharmacists. It is of note that the ERG used a BSA of $1.83m^2$ based upon Australian, not UK, patients who suffered from a variety of cancer types, including prostate and breast cancers. The use of a mean of 1.83 m^2 BSA by the ERG has a critical impact upon the cost per QALY estimate as it leads to the use of a third vial of pemetrexed each cycle – this would not happen in UK clinical practice as the dose would not be increased beyond a BSA of $2.0m^2$, i.e. 2 x 500mg vials, 1000mg of pemetrexed per cycle. The ERG estimates a mean cost of £1768.55 per cycle based on 2.2 vials	The Committee considered the manufacturer's estimate of BSA to be appropriate, but concluded that this factor would not substantially change the ICER

		use per patient, whereas treatment of a patient with a maximum BSA of 2.0m^2 would cost of only £1600 per cycle (£800 per vial).	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	It is not appropriate to apply the same or greater BSC costs to an active chemotherapy arm when comparing pemetrexed to BSC alone. BSC is not used to the same degree in clinical trial populations as active therapy significantly reduces the symptoms that make BSC necessary. There were no differences in symptom benefit between docetaxel and pemetrexed because reduction in key symptoms, including dyspnoea, haemoptysis (bloody cough) and pain were comparable between both therapies. These are the symptoms that would require BSC. It is of note that BSC costs were not applied by the ERG to the erlotinib or docetaxel arm in the current STA or to the docetaxel arm in the previous NICE appraisal for second-line NSCLC. The impact of excluding BSC costs in the active pemetrexed arm is to reduce the incremental cost per QALY for pemetrexed compared with BSC to £44,993, from £59,431 in the ERG calculations, without any other changes to the effectiveness estimates used by ERG.	The Committee concluded that those treated with pemetrexed would receive some underlying supportive care, but that this was plausibly at a lower rate than without active treatment. It concluded that this would not reduce the ICER of pemetrexed by a magnitude for it to be considered cost effective.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource	The comparison of pemetrexed to BSC by the ERG was not based upon the pemetrexed mean survival from the JMEI clinical trial. It is inaccurate to assume a survival benefit of only 1.62 months for pemetrexed compared to BSC (8.76 vs 7.16 months, as in the ERG estimates) when the median survival in the trial was 8.3 months and can be compared to a median of 4.7 months for BSC (Shepherd et al., 2000). Based upon the difference in median survival alone, which is likely to under-estimate the true survival benefit, the incremental cost per QALY would be £23,006 for pemetrexed compared to BSC, assuming a BSA of 1.75m^2.	The Committee considered that the survival estimate for pemetrexed included in the manufacturer's economic model was not appropriate – see FAD section 3.7. It also noted that the mean survival estimate for BSC included in the manufacturer's submission was similar to that found for BSC in the BR21 trial.

	impact and implications for the NHS are appropriate		
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	It is not appropriate to deny the utility benefits of avoiding toxicity through use of pemetrexed, but these were reduced ten-fold to almost zero by the ERG on the basis that the trial had not demonstrated a difference in health-related quality of life (QoL) and efficacy between docetaxel and pemetrexed. There are two reasons why there was no significant difference in QOL between docetaxel and pemetrexed despite the significant reduction in severe toxicities: 1) The Lung Cancer Symptom Scale (LCSS) measures disease symptoms and does not include any assessment of side effects – therefore it does not measure how drug-related toxicity impacts on the patient's QoL. 2) Patients suffering from grade 3 or 4 toxicity do not complete QoL questionnaires so it is difficult to assess the QoL impact of toxicity. The LCSS, in this case, was only administered when patients received treatment, not when they suffered a toxic event. To undermine the utility (QoL) benefit of avoiding life-threatening toxicities goes against all clinical beliefs in the treatment of cancer patients and, in the assessment of two medicines with otherwise comparable efficacy, small differences in utility are known to have a disproportionately large impact on the incremental cost per QALY.	The Committee did not alter the health-related utility estimates from the manufacturer's submission. The Committee noted the data from the LCSS and that it is a measure of lung cancer symptoms rather than treatment related toxicities.
Eli Lilly	whether you consider that all of the relevant evidence has been taken into account	It should be noted that while toxicity-related QoL was not collected in the JMEI trial there is evidence to suggest a toxicity-related QoL benefit with pemetrexed is expected. During an exploratory analysis of JMEI, patients receiving pemetrexed spent significantly longer not experiencing any drug-related blood-toxicity at all compared to docetaxel (mean time: 69.7 days vs 42.3 days), (Bhalla et al 2005). It is reasonable to assume that if patients receiving pemetrexed are spending significantly longer without toxicity this would be translated to a QoL benefit to the patient.	The ERG did not alter the health-related utility estimates from the manufacturer's submission.

Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The efficacy of pemetrexed, based on JMEI, has been called into question by the ERG. Lilly wishes to point out that results from JMEI has been the basis of regulatory approval for pemetrexed in 79 countries worldwide including the European Union and USA on the basis of comparable efficacy to docetaxel. Pemetrexed was granted license by the European Medicines Agency (EMEA) in 2004 for the treatment of patients with second-line NSCLC. The evidence presented to the EMEA included the phase III randomised clinical trial of pemetrexed compared to docetaxel (JMEI). The EMEA EPAR in relation to JMEI states that '...although non-inferiority was not formally demonstrated, the data submitted are robust enough to conclude that a clinically significant inferiority of pemetrexed to docetaxel in terms of efficacy in this population is unlikely". The EMEA go on to state that any possible differences in efficacy between pemetrexed and docetaxel are likely to be marginal. Overall, the benefit/risk ratio of pemetrexed compared to docetaxel puts the two products on the same line given the fact that the efficacy can be considered as similar. The benefit/risk ratio of pemetrexed as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy was favourable, and therefore recommended the granting of the marketing authorisation (EPAR, 2004).	Comments on the ERG report noted.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the	The ERG report [page 25 of 58] discusses a statistical review of JMEI trial undertaken by the FDA quoting the following statement by the FDA "…the study [JMEI] failed to demonstrate superior efficacy as per the trial protocol…failed to demonstrate efficacy based on the fixed margin non-inferiority test as defined in the amended protocol…[and] based on the FDA analysis the study failed to demonstrate efficacy based on the percent retention of control effect non-inferiority testing". In response to these statements, Lilly would refer the ERG back to the FDA and take	Comments on the ERG report noted.

<table>
<tr><td></td><td>preliminary views on the resource impact and implications for the NHS are appropriate</td><td>note of the following statements from the FDA drug approval summary (Cohen et al, 2005) to provide context to the ERG comments:

On Aug 19, 2004, Food and Drug Administration (FDA) granted pemetrexed an accelerated approval as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC who had received prior chemotherapy (Cohen et al, 2005). The accelerated approval was based on the tumour response and the favourable safety profile seen with pemetrexed in the JMEI study. The medical review of the approval signed by Director of the FDA is available on the FDA website.</td><td></td></tr>
<tr><td>Eli Lilly</td><td>Whether all the relevant evidence has been taken into account?</td><td>An updated analysis on the survival data has recently been published. This reflects data available 23 months after the original analysis and after 519 deaths in the study population. These updated survival analyses consistently show that second-line pemetrexed has comparable survival to docetaxel in patients with NSCLC (Demarinis et al, 2006).</td><td>Comments noted.</td></tr>
<tr><td>Eli Lilly</td><td>Whether all the relevant evidence has been taken into account</td><td>Lilly wish to draw attention to two exploratory analyses which further support the FDA statements regarding the favourable safety profile of pemetrexed. In the first, Pujol et al (2005) looked at how long patients survived without experiencing any grade 3/4 toxicities (severe toxicities, most often requiring hospitalisation). The results demonstrated a statistically significant longer toxicity-free survival time for pemetrexed compared with docetaxel. This is clearly a significant benefit for this group of patients.

<table><tr><th></th><th>Pemetrexed (n=265)</th><th>Docetaxel (n=276)</th></tr><tr><td>Median Survival Time</td><td>1.2 months</td><td>0.4 months</td></tr></table></td><td>The Committee were aware of the differences in toxicity profiles of docetaxel in comparison with pemetrexed (see FAD section 4.3).</td></tr>
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<tr><td></td><td></td><td>
<table>
<tr><td>Hazard Ratio</td><td>0.6</td><td></td></tr>
<tr><td>95% CI for HR</td><td>(0.50–0.72)</td><td></td></tr>
<tr><td>p-value</td><td><.0001</td><td></td></tr>
<tr><td>1-year Toxicity-Free Survival</td><td>12.20%</td><td>6.10%</td></tr>
</table>
</td><td></td></tr>
<tr><td>Eli Lilly</td><td>Whether all the relevant evidence has been taken into account</td><td>
In another exploratory analysis of JMEI looking at burden that drug-related toxicities have on patients, Bhalla et al (2005) found that patients receiving pemetrexed spent significantly longer not experiencing any drug-related toxicity (grade 1-4) at all compared to docetaxel. The differences are more pronounced with high grade toxicities which are considered severe and life-threatening. It is reasonable to assume that if patients receiving pemetrexed are spending significantly longer without drug-related toxicity this would be translated to a QoL benefit to the patient.

Toxicity burden to be borne by the average patient in JMEI (Bhalla, 2005)
<table>
<tr><td></td><td>Mean time (days)
Docetaxel
238 patients</td><td>Pemetrexed
212 patients</td><td>P-value</td></tr>
<tr><td>Haematological toxicity grade</td><td></td><td></td><td></td></tr>
<tr><td>Time spent receiving chemotherapy</td><td>77.9</td><td>88.8</td><td>0.278</td></tr>
<tr><td>Time with no drug-related toxicity</td><td>42.3</td><td>69.7</td><td><0.001</td></tr>
<tr><td>Time with toxicity Grade 1</td><td>5.2</td><td>7.6</td><td>0.688</td></tr>
<tr><td>Time with toxicity Grade 2</td><td>5.5</td><td>8.5</td><td>0.587</td></tr>
<tr><td>Time with toxicity Grade 3</td><td>10</td><td>2.1</td><td><0.001</td></tr>
<tr><td>Time with toxicity Grade 4</td><td>14.9</td><td>0.9</td><td><0.001</td></tr>
<tr><td>Non-Haematological toxicity grade</td><td></td><td></td><td></td></tr>
<tr><td>Time with no drug-related toxicity</td><td>16.4</td><td>22.8</td><td>0.04</td></tr>
<tr><td>Time with toxicity Grade 1</td><td>21.6</td><td>32.9</td><td>0.027</td></tr>
<tr><td>Time with toxicity Grade 2</td><td>28.3</td><td>28.3</td><td>0.39</td></tr>
<tr><td>Time with toxicity Grade 3</td><td>10.3</td><td>4.6</td><td>0.001</td></tr>
</table>
</td><td>The Committee were aware of the differences in toxicity profiles of docetaxel in comparison with pemetrexed (see FAD section 4.3).</td></tr>
</table>

		Time with toxicity Grade 4 1.2 0.3 0.02	
Eli Lilly	Whether all the relevant evidence has been taken into account	Section 4.4 of the ACD discusses that only patients who experience allergic reactions to docetaxel would be considered for pemetrexed. Based on a survey including over 70 clinical oncologists, medical oncologists and chest physicians, 82% stated that docetaxel has treatment limiting side-effects (Lilly Data on File, 2006).	The Committee considered the possible role of pemetrexed for people for whom docetaxel therapy is unsuitable. However, after careful consideration of all the evidence, the Committee concluded that pemetrexed should not be recommended for these people (see FAD sections 4.8-4.12)
Eli Lilly	Whether all the relevant evidence has been taken into account	Lastly, the reason some patients are not suitable for docetaxel is the high incidence of grade 3/4 toxicities. With respect to treatment of non-haematological toxicities such as nausea, vomiting and diarrhoea, patients need IV fluids, parenteral nutrition, and in some cases patients need to be admitted to an intensive care unit (see Chemotherapy Pathway Document obtained from local Hampshire hospital, Appendix 1). Severe alopecia (severe and total hair loss), however is irreversible. The impact of toxicities on the patients QoL should not be underestimated given palliative aim of treatment in advance lung cancer.	The Committee were aware of the differences in toxicity profiles of docetaxel in comparison with pemetrexed (see FAD section 4.3).
Eli Lilly	Whether the summaries of clinical and cost effectiveness	The Evidence Review Group Report (ERGR) on pemetrexed on page 8 [of 58] states 'the methods used to perform the indirect comparison were considered by the evidence review group to be inappropriate. The results obtained by the methods employed cannot be considered reliable or	Comments on the ERG report noted. The Committee carefully

	are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	meaningful, since they effectively undermine all of the benefits of randomization inherent in the source trials and do not adjust for the resulting imbalances between the pooled comparators. The only direct and reliable clinical evidence available, which is relevant to the reference case of this appraisal, is therefore the JMEI trial of pemetrexed versus docetaxel'. It is important that the terminology used here is sufficiently defined. Use of the generic term 'indirect' comparison needs to be further disaggregated, in order to better understand the nature of the ERG concerns. Indirect comparisons present in two forms - adjusted and unadjusted. An adjusted indirect comparison is a comparison of a single treatment that is adjusted by the results of a direct comparison with a common control group, partially using the strength of the RCT. Adjusted indirect comparisons can only be performed where there is a common treatment that links one clinical trial to another, such as a placebo. An unadjusted indirect comparison is the term given to an analysis where data on the absolute values are pooled across treatment arms or taken as single estimates. This latter form of treatment comparison is typically reserved for situations where an adjusted indirect comparison is not permissible, due to the absence of trials that provide linkages between treatments, such as in the recent case of the NICE submission on gemcitabine as a treatment for metastatic breast cancer. The Lilly submission on pemetrexed presented an economic model to the ERG that allowed users (of the model) to perform either form of indirect comparison (adjusted or unadjusted) in keeping with the agreed scope of the NICE Decision Problem; that being to compare pemetrexed against docetaxel, erlotinib and BSC. A direct comparison, on the other hand, using data from a head-to-head comparison of pemetrexed versus docetaxel in the JMEI trial, as advised by the ERG, would have failed to incorporate two of the comparator arms in the agreed Decision Problem,	considered both approaches to indirect comparison presented.

		BSC and erlotinib, as well as four additional phase III RCTs available on docetaxel.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The ERG did not adhere to the scope of the agreed Decision Problem when reviewing the Lilly submission on pemetrexed. They neither made it known within their evidence review report that the cost-effectiveness of pemetrexed had in fact been determined using both methods of indirect comparison. The ERG claimed that the methods employed were inappropriate, despite the Decision Problem agreed by NICE prior to the Lilly submission clearly stating the need to compare pemetrexed to other second-line treatments that included BSC as well as docetaxel and erlotinib. The methods adopted by Lilly were thus entirely justified and appropriate for the Decision Problem in question.	Comments on ERG report noted. Both analyses submitted by the manufacturer were carefully reviewed by the Committee. Details of both analyses have been referred to in the FAD (section 3.7) and pre-meeting briefing (section 3.3.2).
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for	Page 29 [of 58] of the ERGR on pemetrexed contains the statements 'the company submission does refer to the Bucher indirect method but the method has not been applied correctly since treatment arm level data have been used instead of (log) hazard ratio estimates' and 'the company submission does not use an adjusted indirect comparison'. Not only does the economic model permit both types of indirect comparison (as explained above) but the results of the adjusted indirect comparison are presented in the sensitivity analyses in the submission document.	It discussed both the base case analysis based on an unadjusted indirect comparison of pooled absolute survival estimates from several trials, and a sensitivity analysis based on adjusted indirect comparison of pooled hazard rates from several trials. It considered both indirect comparisons inappropriate given the inconsistency of the findings in relation to the direct

	the NHS are appropriate		randomised comparison between pemetrexed and docetaxel.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The economic case for erlotinib described in the submission by Roche focused on a comparison against docetaxel (their chosen comparator) that employed an unadjusted method of indirect comparison alone. The opportunity did exist to perform an adjusted indirect comparison using data on erlotinib from the BR21 trial (Shepherd et al., 2005) and data from the randomised controlled trial of docetaxel vs. BSC reported by Shepherd et al., (2000) - using the BSC arm as the treatment linking the two treatments to one another. Therefore, Lilly find it surprising that there is no mention in the ERG report on erlotinib on the importance and appropriateness of using the Shepherd et al., (2000) trial to link erlotinib to docetaxel using BSC as the treatment link despite the Shepherd et al., (2000) trial being a pivotal phase III clinical trial in the published evidence base for docetaxel.	Comment on ERG report noted.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are	The ERG having questioned the efficacy of pemetrexed vs. docetaxel based on the head-to-head JMEI trial, re-calculated a cost per QALY for pemetrexed compared to docetaxel by substituting existing values for overall survival contained within the economic model with the absolute values for overall median survival for docetaxel reported in the JMEI trial. In doing so, the ERG make the assumption that pemetrexed achieves the same overall survival as docetaxel (which is 34.23 weeks). The ERG reported a cost per QALY of £458,333. However, when the same task was repeated by Lilly, the cost per QALY produced was £164,956	Comment on ERG report noted.

	appropriate		
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	In addition to modifying the estimates for overall survival in an attempt to replicate the cost of £1,129,123 per QALY reported in the ERGR on pemetrexed, the Lilly Health Outcomes Team further changed the following variables in their model: ▪ Time to disease progression for pemetrexed to equate to the same as docetaxel (using data reported in the JMEI trial) ▪ Overall response rates for pemetrexed to equate to the same as docetaxel (using data reported in the JMEI trial) ▪ Adverse events rates to reflect the profile for each product as observed in the JMEI trial ▪ Treatment discontinuation rates due to adverse events to reflect the same in the JMEI trial for docetaxel; and ▪ Employed a half-cycle correction in the model for the adverse events. Introducing these changes increased the cost per QALY for pemetrexed compared to docetaxel to £243,609.	Comment on ERG report noted.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource	Further changes to the assumptions of the model that included the following, made very little difference to the above cost per QALY, although the justification for questioning the original assumptions employed in the model cannot be reliably substantiated. ▪ Changing the body surface area used to perform the chemotherapy drug calculations from $1.7m^2$ to $1.83m^2$; ▪ Changing the maximum number of chemotherapy cycles in the model, despite the fact that the median number of cycles within the economic model was 4; ▪ Using per vial as opposed to per mg costing;	Comment on ERG report noted. After carefully considering the available evidence, the Committee concluded that pemetrexed had not demonstrated superior survival to docetaxel.

	impact and implications for the NHS are appropriate	▪ Changing the unit cost of febrile neutropenia to £2,257.50; ▪ Assuming 10.6% of patients receiving pemetrexed require an in-patient stay and 13.9% of patients receiving docetaxel the same; ▪ Assuming admitted patients have 2 journeys per cycle from the hospital to the chemotherapy centre for pemetrexed and docetaxel. These high costs per QALY assume clinical equivalence however which is not a valid assumption based on the clinical trial evidence of JMEI.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The ERG report on page 44 [of 58] states that the overall utility gains were also re-estimated for pemetrexed over docetaxel to produce their cost per QALY of £458,333, however it is not clear how these calculations were performed. When Lilly requested clarification from NICE so that they too could replicate this analysis, the response dated 15th November 2006 was that 'having checked with the technical team on this occasion, the ERG has not made adjustments to the 'utility data' when presenting their illustrative scenario'.	The ERG did not amend the health-related utility estimates included in the manufacturer's submission. Amendments were however made to the assumptions regarding survival and a half cycle correction was introduced. See ERG report.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations	Further, there is a lack of transparency on how the ERG has applied their adjustments to the number of treatment cycles with pemetrexed and docetaxel. The model provided by Lilly is based on a maximum of 6 cycles (as most patients in clinical practice receive up to 4 cycles of chemotherapy). In the JMEI trial, 96.7% of patients treated with pemetrexed had responded (complete or partial response) by cycle 6 and	Comments on ERG report noted. The ERG analysis assumed that the number of cycles would be as reported in the JMEI trial.

	of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	less than 20% of patients on pemetrexed continued to receive chemotherapy beyond cycle 6. Lilly were therefore unable to reliably determine due to the lack of transparency in the ERG methods how the cost of £1,129,123 per QALY calculation had been performed. It is most unlikely that this cost was estimated using the Lilly economic model correctly.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	Acquisition cost of pemetrexed The acquisition cost of pemetrexed in section 2.4 of the ACD is listed as £8000 for a typical course of treatment. A typical course of treatment will range between 3-4 cycles of pemetrexed which equates to £4,800-£6,400. This cost assumes vial wastage and is based on varying body surface area for patients.	The FAD has been amended.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the	Coverage of databases employed in the systematic literature review Lilly undertook a systematic review of the literature in order to identify relevant phase III clinical trials for use in their Lilly submission on pemetrexed, which fulfilled the NICE STA requirements. The ERG criticise the review in claiming [page 18 of 58] that 'other relevant databases and conference sites were not searched such as the Web of	Comments on the ERG report noted.

	preliminary views on the resource impact and implications for the NHS are appropriate	Science, ISI Proceedings and the European Society for Medical Oncology (ESMO) proceedings'. In addition to adhering to the NICE STA requirements, Lilly consulted the health technology assessment (HTA) report by Royle & Waugh (2003) entitled 'Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system' which clearly state that 'searching additional databases beyond the Cochrane Library (which includes CCTR, NHS EED and the HTA database), MEDLINE, EMBASE and SCI, plus BIOSIS limited to meeting abstracts only, is seldom effective in retrieving additional studies for inclusion in the clinical and cost-effectiveness sections of TARs (apart from reviews of cancer therapies, where a search of the ASCO database is recommended). A more selective approach to database searching would suffice in most cases'. The coverage of databases employed in the Lilly submission on pemetrexed can thus unequivocally be deemed complete and appropriate.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are	Methods employed with respect to the reporting of data from the systematic review of the economic evidence The ERGR [page 33 of 58] claims that 'data were extracted on title, aims and methods, results and relevance to decision-making in England and Wales. Both forms of data extraction are simplistic and do not provide sufficient details for a comprehensive comparison of studies'. Lilly are concerned that the ERG were not familiar with the requirements of the NICE STA form under Section 3.1.2 entitled 'Description of Identified Studies' that asks manufacturers to 'provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales'. Nevertheless, Lilly believe they have completed the STA form as stipulated by NICE and hope the ERG will	Comments on the ERG report noted.

	appropriate	recognise this part of the NICE STA form requirement.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	Trial Characteristics Page 21 [of 67] of the ERGR on pemetrexed refers to the pivotal clinical trial of pemetrexed and states that 'the mean number of patients per site is 4 (125 centres from 23 countries). Such contextual diversity and small numbers may undermine some of the benefits of randomization, and also cast doubt on the applicability of results to any one country'. Assessment of the external validity of data obtained from randomized controlled trials is a well documented problem. Nevertheless, this form of scientific evidence represents the highest quality for use in clinical evaluations. There is no evidence to support the notion that the results of the JMEI trial cannot be generalised to the UK. Accepting the ERG's argument implies that all data obtained from multi-centre, multinational RCTs are redundant by virtue of the fact that none of the results apply to any one country, which is not realistic.	Comments on the ERG report noted.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource	Critique of the Lilly Company Model Lilly developed a multi-state transitory Markov model to perform the economic evaluation of pemetrexed compared to relevant comparator therapies in the second-line treatment setting. This model incorporated the effect of treatment on overall survival, time to disease progression and importantly, the effect of a wide range of adverse events using utility values obtained from the largest and most comprehensive study performed to date in NSCLC. Expert clinical opinion was sought throughout the evaluation to guide the design of the model, the underlying structural assumptions and the configuration of treatment	Comments on the ERG report noted.

	impact and implications for the NHS are appropriate	algorithms used for both the administration of chemotherapy and treatment of serious adverse events. The model reflected all of the important costs and clinically meaningful outcomes associated with the disease and its treatment. As such, it scored very highly against common check-lists for economic evaluation methods and adhered to the framework for good practice in modelling proposed by Philips et al., (2004). The design of this model has been successfully employed in metastatic breast cancer and is the most sophisticated model to date produced for evaluating treatments in NSCLC.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The ERGR [page 34 of 58] make the following statements: ▪ Side effects in the company model appear to be restricted to treatment-related events only. Side-effects are dealt with in the Lilly submission as treatment-related adverse events, not disease symptoms. Lilly are interested to understand what the ERG would consider to be side-effects of the different treatments that are not, as they describe, treatment-related	Comments on the ERG report noted.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations	The ERGR [page 34 of 58] make the following statements: ▪ Death only occurs in the progressive health state or for patients experiencing febrile neutropenia. Lilly fail to see the rationale for over-complicating the model by	Comments on the ERG report noted.

	of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	introducing random events such as deaths not occurring as a result of disease progression or serious adverse events. These two causes of death are the two most likely causes amongst this patient population, which is the reason why they have been used in the model.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The ERGR [page 34 of 58] make the following statements ▪ The model does not allow for patients to die of anything other than cancer, or treatment-related causes, which is an unrealistic assumption. If the economic model was to allow for patients to die of anything other than cancer or treatment-related causes, then it would be impossible to reliably determine which of the treatments under evaluation were the most effective or cost-effective. Inclusion of data of this sort would bias against treatments where, for example, patients were involved in road traffic accidents. It is not appropriate or reasonable to introduce this kind of 'noise' into the model.	Comments on the ERG report noted.
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the	▪ Drug administration costs The ERG criticise Lilly for not employing the full daily cost of chemotherapy administration in the model for each treatment, despite the fact that patients spend variable amounts of time receiving their treatment because of differences in the administration times between docetaxel and pemetrexed. The differences in administration times are not irrelevant on the grounds that hospitals are reimbursed for their costs according to a	Comments on the ERG report noted.

	preliminary views on the resource impact and implications for the NHS are appropriate	reference or tariff cost so such differences do matter. Hospitals are still required to make use of treatment pathways to avoid bottle-necks in the system and opt for cost-minimizing practices where appropriate. The economic model produced by Lilly uses the tariff as a basis for estimating hourly costs of treatment but does allow for differences in administration times. There is no evidence to support the ERG assumption that patients require transportation to and from hospital to a chemotherapy centre to receive treatment and furthermore does not differentiate between docetaxel or pemetrexed.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	Cost estimates for febrile neutropenia The ERG substitute the published cost estimate for febrile neutropenia contained within the economic model with their own cost estimate that they calculate using an un-validated treatment algorithm populated with unit costs that are at least two years out of date. It is thus not surprising that the resultant cost would be lower than that used in the economic model however there are no valid grounds for questioning the accuracy of the original unit cost estimate used. This estimate was included in the Lilly submission, the erlotinib submission and in the original appraisal of docetaxel in second-line NSCLC.	Comments on the ERG report noted. The Committee carefully considered the likely cost of treating febrile neutropenia. (See FAD section 4.7).
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations	Approval of pemetrexed by other bodies The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia approved pemetrexed for NSCLC in November 2004 and pemetrexed is currently under review by the Scottish Medicines Consortium (SMC). The ERG state [page 14 of 58] 'pemetrexed has not been reviewed by the	Comment noted

	of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	Scottish Medicines Consortium (SMC) despite the company being asked on several occasions to make a submission. The SMC viewed the company's decision not to submit as a failure to prove their case for pemetrexed and hence the medicine was not recommended for use in Scotland'. Lilly can confirm that further to a single request from the SMC, we have made a submission to SMC. The decision not to submit previously was based upon the very low numbers of eligible patients anticipated in Scotland – as was communicated to the SMC by Lilly. In a teleconference with NICE and Lilly earlier this year, Lilly clarified this point with NICE and we are therefore surprised at this statement by the ERG.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	The phase III registration trial (JMEI) demonstrated comparable efficacy between pemetrexed and docetaxel but there were significant safety advantages of pemetrexed over docetaxel including febrile neutropenia and hospitalisation due to febrile neutropenia, and certain severe and life-threatening non-haematologic toxicities such as nausea/vomiting/diarrhoea	The Committee were aware of the differences in toxicity profiles of docetaxel in comparison with pemetrexed (see FAD section 3.3).
Eli Lilly	Whether the summaries of	With regards to the economic evaluation, we trust that our comments have demonstrated that the estimates produced by the ERG should be	Comment noted

	clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	viewed with caution because: ▪ We could not replicate the results produced by the ERG despite incorporating the adjustments the ERG state have been made and; ▪ The variables and assumptions underpinning the economic model have been subjected by the ERG to the most unlikely range of scenarios and use of alternative input values that neither reflect clinical practice / opinion nor reflect the costs and consequences of the likely implications of the product's use.	
Eli Lilly	Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate	In the Lilly submission, pemetrexed was clearly positioned as an alternative option to docetaxel in the following circumstances, where Best Supportive Care would be the current option: ▪ if the patient has received docetaxel or paclitaxel first-line and cannot be re-exposed to a taxane, ▪ if the patient is allergic to or unable to tolerate docetaxel and yet is suitable for active chemotherapy ▪ if the physician and/or patient have significant concerns regarding toxicity associated with docetaxel.	Comment noted