Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	National Lung Cancer Forum for Nurses committee member
Location	Wales
Conflict	no
Notes	This response from the National Lung Cancer Forum for Nurses who represent 260 Lung Cancer Nurse Specialists throughout the UK.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	see section 4
Section 2 (The technology)	see section 4
Section 3 (The manufacturer's submission)	see section 4
Section 4 (Consideration of the evidence)	4.23 From a working clinical perspective, the majority of patients who are diagnosed with Non Squamous NSCLC generally receive Pemetrexed with Capsulation or Carboplatin. This group would therefore be eligible, if fit enough, for Pemetrexed maintenance therapy. Patients who receive any other chemotherapy agent other than Pemetrexed ie Gemcitabine, Paclitaxel (with Cisplatin or Carboplatin) would not, as far as our understanding goes, be eligible for Pemetrexed maintenance therapy. Therefore the analysis from the appraisal, which mentions switch maintenance, is not relevant. The NLCFN would therefore assume that the numbers of patients eligible are greatly reduced. For the End of Life Criteria this is very important to consider. 4.24 Also relevant to the above comments, it could be recognised that those patients eligible for second line Pemetrexed have been overestimated. You have stated that patients who did not receive Pemetrexed as induction or maintenance of would be potentially eligible for second line chemotherapy following disease progression. However, the number of patients (1500) that you have quoted who might be eligible for second line therapy (one third of PS 2) appears high from our perspective. In addition we think that the point raised in 4.23 needs clarification as if patients have had Pemetrexed therapy first line then they would not be eligible second line. This again significantly impacts total patient numbers and hence eligibility of End of Life Criteria. Cost Effectiveness 4.10 Whilst we recognise that you have focused on only one mode of surveillance with CT follow up based on the Paramount study we are sure that there will be clinical variation (based on clinician preference) to detect recurrence. Chest x-rays can be utilised as routine in follow up with CT requested if there are concerns from CXR or patient reported symptoms.

	Patients on maintenance treatment could be followed up in Lung Cancer Nurse Specialist led clinics rather than the traditional medical led clinic. Lung Cancer Nurse Specialists are skilled practitioners who will know the patient well and are highly likely to detect early signs of recurrence through recognition of concerning symptoms. Patients have access to Lung Cancer Nurse Specialists for advice and access to be reviewed in clinic at any time in event of problems with disease progression often identified via this line of follow up. These modes of follow up have been identified as effective in terms of detecting recurrence and acceptable to patients. Internal audits of practice within Lung Cancer Units have demonstrated this. This again will reduce the cost of providing Pemetrexed as maintenance therapy. We would also like to highlight the importance of the quality of life for patients receiving maintenance Pemetrexed therapy. From our perspective maintenance therapy will potentially delay the onset of distressing symptoms, reduce hospital visits, a reduction of inpatient stays and a reduction of prescriptive medications (and associated costs). This is hugely important from a nursing perspective and takes into account the associated impact on community services. Our final comment is with regards to the historical lack of treatment options for patients with lung cancer. The initial studies into lung cancer chemotherapy did not show major differences in survival but the clinical community has gradually increased its knowledge, understanding and clinical application in the delivery of chemotherapy and novel agents. We welcome new agents into the practice. Pemetrexed has proven to be an effective chemotherapy agent in the first line setting, well tolerated, with the potential to deliver good response rates. We would like to see this available as a maintenance therapy to offer as a therapeutic option for our patient population and hope that you take our comments into consideration.
Date	02/04/2013 17:22

Name	[redacted]
Role	NHS Professional
Location	England
Conflict	no
Notes	Speaker and advisory board fees
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Several errors in the preliminary recommendations reduce the cost effectiveness and have overestimated the patient numbers (excluding end of life consideration).Worryingly comments on age eg 3.14,4.6etc reveal a bias for doubting the applicability of the results to our patient population, there is no evidence that age is a prognostic nor predictive factor for NSCLC chemotherapy. The economic assessments eg 3.20 3.21, 4.15, based on the post hoc use of an adjusted model when there was no baseline patient imbalance and PFS secondary calculations eg 3.19 with the attendant observer variability,

	rather than the definitive OS endpoint are a very questionable, unreliable approach. There is double counting 4.21 - 4.23, for the patient number likely to receive pemetrexed as switch maintenance would not be prescribed as first line pemetrexed platinum is given routinely in the UK. No pemetrexed is used 2nd line 4.24 as it is not approved by NICE and counting these invisible patients is a specious argument which is clinically meaningless .Using currently available data the expected total patient population would be <8000 ~7000.The appraisal is likely to be positive for providing a more objective, clinically meaningful approach is taken
Section 2 (The technology)	Pemetrexed is an important new cytotoxic which has benefitted advanced NSCLC patients in terms of clinically important increases in overall survival with no quality of life detriment due to a milder side effect profile. Extending the benefits of pemetrexed with continuous maintenance for people with advanced NSCLC would help reduce a serious unmet need
Section 3 (The manufacturer's submission)	3.14 These comments are irrelevant as patients would only be treated if PS0 1, age is not prognostic, predictive, and stage IV has increased in trials because of the new TNM classification. 3.16 where is the evidence for ERG`s criticism based on the 8 parameters eg BSA .3.17 given there was no baseline imbalance insisting on an adjusted model equates to post hoc prejudicial fitting of data to an ERG preferred model 3.18 why use a common survival when the trial survival was so different, extrapolating at the end of the survival curves with ~30 patients overall introduces wider confidence limits and is more unreliable than using all the survival data from the start. The approach has no clinical value.3.19 A plausible explanation is selection of more slowly growing clones, the faster ones being more sensitive to CT. 3.21 scenario 4 the post hoc reasoning for an adjusted model just because it reduces an assumed post progression survival, which in turn is based on CT scan interpretation introduces many unnecessary assumptions and questions the validity and clinical relevance of such an approach
Section 4 (Consideration of the evidence)	4.6 Only PS0/1 patients entered the trial and PS01 non trial patients would be expected to behave similarly 4.8 It should be noted that in Paramount EQ5D was used a generic questionnaire and not sensitive to lung cancer specific symptoms as in FACT L where there was an improvement in the switch maintenance trial. 4.10 Follow up appointments are the same, every 6-8 weeks as recommended in guidelines but is often much shorter due to the rapid progression <2 months with serious symptom logy with a wait and watch policy, these patient need similar if not more hospital interventions. The median number of five pemetrexed cycles argues at the most one extra CT scan will be at a six week interval. 4.12

	The trial data did show reduction in subsequent treatment in the pemetrexed arm particularly in the erlotinib 6% and docetaxel 6% treatments. Choosing t o disregard these data as non-significant where no such restriction exists in the economic adjusted analysis is untenable 4.13 Disagree given the above. 4.14 There is no reason to use an adjusted model as no imbalance in the pre-treatment characteristics and age is not a prognostic independent significant factor The ERG`s post hoc analysis tagged onto the end of the survival curves will of course be less robust than examining the whole of the survival curve. The post hoc fitting of the ERGs adjusted model is unscientific and clinically inappropriate. 4.15 The cut points of 20% is reasonable clinically, larger numbers are always preferable to smaller numbers 4.20 It must be noted that in the UK pemetrexed is not used the second line setting, NICE guidance and therefore does not contribute to the patients actually treated in this end of life criteria 4.23 Double counting, pemetrexed switch maintenance trial is no longer relevant, given the widespread UK use of 1st line pemetrexed Here market research data are used (although not used for the second line indication (below), zero in the UK. Therefore, 535 is a reasonable number. 4.24 Second line pemetrexed PS0-2 is not NHS funded, erlotinib which is funded would be used, 4.27 End of life criteria would be fulfilled if corrections to the assumptions re numbers are made
Date	25/03/2013 10:33

Name	[redacted]
Role	NHS Professional
Location	England
Conflict	yes
Comments on individual sections of the ACD:	
Section 3 (The manufacturer's submission)	Re 3.7 it should be noted that no patients received 2nd line pemetrexed. Re 3.14 The non-squamous NSCLC group occur in a younger, female predominant, better performance status with fewer ever smokers. In my opinion the trial population is consistent with my patient population.
Section 4 (Consideration of the	Re 4.23 It is an incorrect assumption to state that an equal number of patients will be eligible for switch maintenance. The

evidence)	majority of patients will be continuous maintenance Re 4.24 This assumption is grossly flawed. Note my earlier comment re 3.7 Re 4.25 This estimate is grossly flawed as a significant proportion of patients are PS 2 or worse and so unfit for chemotherapy. Re 4.26 based on my comments I request that the committee reconsider this point.
Date	14/03/2013 00:24

Name	[redacted]
Role	NHS Professional
Location	England
Conflict	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Unfortunate grammar in wording of 1.1. On first reading it would appear that the guidance is recommending pemetrexed for use in squamous cell tumours. I know you have to use licenced indication but not at the expense of clarity and reasonable English. My other comments fed back to NCRI CSG so not included here.
Date	13/03/2013 15:30

Name	[redacted]
Role	NHS Professional
Other role	Health Professional (Private)
Location	England
Conflict	yes
Notes	Contributor to PARAMOUNT Trial
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	1.1 Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than predominantly squamous cell histology in people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin. The wording of this paragraph can be interpreted as implying that Pemetrexed maintenance is recommended for squamous cell histology in non-progressing cases. This is clearly not the case and the wording should be amended to avoid confusion.
Section 2 (The technology)	The demonstration of the specific activity of pemetrexed in nonsquamous cell histology NSCLC is, I believe, a significant advance in the management of this unfortunate group of patients. I say this as a medical oncologist who has published trials in this field over more than 20 years. It is an agent that is tolerated much better than competitors and, remarkably, is associated with almost no cumulative toxicity. Thus these patients, who include the life-long non-smoking lung cancer cases, are enjoying longer survival with fewer sife-effects.

Section 4 (Consideration of the evidence)	There are, I believe errors in the calculation of population sizes for Pemetrexed in 4.24. Since the data for second line therapy, switch maintenance and continuation maintenance became available at different times over the last few years an assumption has been made in the ACD that all three settings might be appropriate for an individual patient. This is not the case. Firstly, the patients likely to be offered continuation maintenance will not have been eligible for switch maintenance and vice versa, so in practice they will be the same 500 or so patients. These days, with the increasing use of first line Pemetrexed+cisplatin in non-squamous NSCLC they will all be offered continuation maintenance if eligible and therefore will not ever be eligible for switch maintenance. Similarly, patients who have had 1st line pemetrexed will not be receiving 2nd line with the same drug whether or not they have had continuation maintenance. So here again there has been double-counting. I believe this should make a significant reduction to the total number of patients eligible for, and receiving the drug.
Date	05/03/2013 20:10