NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
AstraZeneca	Section 2.4 and 4.17: AstraZeneca welcomes the comments made by the Appraisal Committee relating to the likely simple administration of the proposed patient access scheme in the NHS.	Comment noted
AstraZeneca	Section 4.2: AstraZeneca welcomes the Committee's comments that pemetrexed/cisplatin should be used as the main comparator of interest in this appraisal since it is likely to become standard of care for previously untreated non-squamous NSCLC patients (TA181).	Comment noted
AstraZeneca	Section 4.3: AstraZeneca welcomes Committee's views on the implementation of EGFR-TK mutation testing not being a limiting factor for the NHS.	Comment noted
AstraZeneca	Section 4.8: From AstraZeneca's own experience of EGFR mutation testing in the United Kingdom, 342 tests reported with 59 mutations found (17.25%) from 7 testing centres across the United Kingdom. The Manufacturer presents this information in further detail in the response to the Appraisal Committee's questions.	The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be between 10% to and 15% in the target population. Please see FAD section 4.16.
AstraZeneca	Section 4.9: AstraZeneca supports the view of the appraisal committee that standard combination therapies have very similar (but not equivalent) efficacy. It should be clarified that pemetrexed/cisplatin has significant benefits in OS only as the current text in the ACD implies benefit in OS and PFS against standard combination therapy in a non-squamous population. In addition, AstraZeneca supports the view that the currently immature OS data for gefitinib is similar to pemetrexed/cisplatin and that gefitinib has significantly higher PFS than pemetrexed/cisplatin and standard combination therapies.	Section 4.9 of the FAD has been updated accordingly.
AstraZeneca	Section 4.11: AstraZeneca looks forward to sharing with the Committee the additional requested analyses for the Overall Survival estimates. However AstraZeneca does not routinely share individual patient level data with third party organisations.	Comment noted.
AstraZeneca	Section 4.12: AstraZeneca welcomes the views of the individual clinical specialists	The Committee accepted the evidence from the

Consultee	Comment	Response
	that previously untreated NSCLC patients can be treated with up to 6 cycles if the patient responds to treatment. This is in line with ESMO and ASCO clinical guidelines which recommend 4-6 cycles of chemotherapy and also NICE clinical guidelines which do not state a maximum number of cycles.	clinical specialists and consultees that patients often receive five and increasingly six cycles of chemotherapy (because of the availability of better anti-emetics and improved tolerability). (See FAD section 4.14 & 4.15).
AstraZeneca	Section 4.14: Since the publication of the ACD, AstraZeneca has spoken to twelve Oncologists and Pathologists concerning repeat biopsy rates. The consensus was only 2-3% of specimens need to be rebiopsied. This low biopsy rate has largely been attributed to the hisotlogical diagnosis required before pemetrexed/cisplatin can be prescribed. Histological diagnosis requires a bigger sample size than EGFR mutation testing.	Costs related to biopsy and the possible need for repeat biopsy are not included in the FAD.
AstraZeneca	Section 4.18: The criteria for End of Life supplementary advice states in 2.3.1: 'The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival' In the Appraisal Consultation Document (ACD), the Committee states that it has concerns that gefitinib has not shown a survival advantage over pemetrexed/cisplatin. Whilst AstraZeneca would agree that there has not been a trial comparing gefitinib to pemetrexed/cisplatin however the AZ submission provides indirect evidence from the Network Meta-Analysis (NMA) and the Weibull regression analysis where paclitaxel/carboplatin was used as a baseline. In this analysis conducted following the Guidance to Manufacturers gefitinib demonstrated a progression-free survival advantage of 3.4 months over pemetrexed/cisplatin.	Please see section 4.20 of the FAD. The Committee agreed that it was no longer necessary to follow the supplementary advice from NICE that is taken into account when appraising treatments which may extend the life of patients with a short life expectancy and which are licensed for indications that affect small numbers of people with incurable illnesses. This was because, following consultation and the revised analyses, the most plausible ICERs fell below the threshold normally considered to be a cost-effective use of NHS resources.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal. We would like to submit the following comment; Lung Cancer Specialist Oncologists in Wales are very disappointed with NICE's proposal not to recommend gefitinib for use in the NHS. 80% of patients do not survive a year and up until now, with the development of targeted therapies, oncologists have not been able to predict which patients will respond to chemotherapy - less than 50% of those are treated derive any benefit. Compared to patients on chemotherapy, patients on gefitinib are far more likely to; 1. Have their cancers shrink (response rate 75% with gefitinib vs. 43% with	Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.

Consultee	Comment	Response
	chemotherapy) 2. Have a better quality of life and 3. Have fewer side effects With gefitinib, we have a targeted therapy that works in 75% of patients whose tumours show mutation of EGFR. The data indicate that for this small group of patients (10% of NSCLC) gefitinib is a major advance over standard chemotherapy being both more effective and less toxic. The introduction of gefitinib as 1st line therapy would allow effective sequencing of the drugs that are available. Patients would be spared ineffective treatment and thus save NHS costs. Specifically, patients receiving gefitinib will not get second line erlotinib which is the NICE approved second treatment of choice for these patients. It is difficult therefore for the clinician to accept the NICE appraisal and continue with the current treatment pathways.	
Royal College of Nursing	The RCN welcomes the opportunity to comment on this document and responds below to the four questions on which comments were requested: i) Has the relevant evidence been taken into account? The evidence to date that has been considered by the appraisal committee appears to be comprehensive. ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate? There are no specific comments to make in this section at this stage. iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? Nurses caring for this group of patients welcome the development of and access to Gefitinib. This provides a truly targeted treatment option with previously unseen	Comment noted Comment noted Gefitinib is now recommended when specific criteria

Consultee	Comment	Response
	survival benefits for a group of lung cancer patients. The technology is a very well tolerated treatment that is easily administered orally. The patient does not need to attend hospital too frequently. The technology is a welcomed option for treatment in lung cancer. iv) Are there any equality related issues that need special consideration that are not covered in the ACD? We are not aware of any equality issues that have been missed at this stage.	are met. See section 1 of the FAD. Comment noted
British Thoracic Society Lung cancer and Mesothelioma Specialist Advisory group	Thanks for giving us the opportunity to comment on this consultation document. We are not aware of any data that has not been included in this extensive analysis. Whilst we acknowledge that there are ongoing discussions regarding the cost-effectiveness of first-line Gefitinib, we must not forget that for some patients, this treatment can offer very substantial improvements in both survival and quality of life, with minimal toxicity. We feel it would be a huge missed opportunity if such patients are to be denied this option in the future. Therefore we would encourage NICE to seek a place for this therapy in selected patients.	Comment noted Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD. .
Cancer Research UK	Cancer Research UK welcomes the opportunity to respond to this consultation. However, we are very disappointed that NICE do not feel able to recommend gefitinib (Iressa) for patients with non-small cell lung cancer. <u>Gefitinib as a targeted treatment:</u> Gefitinib provides a good example of how advances in medical research have led to a more individualised approach to cancer treatment. We know that this drug only works in patients with a specific genetic mutation. Treating only the patients that will respond to this drug will not only mean that many patients won't have to undergo unnecessary treatments, but should save the NHS money in the long term. The ability to classify individuals into sub-populations that differ in their response to a specific treatment means that patients will get more effective treatments, with fewer side effects, and the NHS will improve prescription cost-effectiveness. However, we are concerned that NICE hasn't taken the benefits of this stratified approach adequately into consideration when conducting their appraisal. <u>Potential cost-savings of targeting treatment:</u> EGFR testing is an excellent way of targeting treatment to a minority of patients with mutEGFR non-small cell lung cancer. There is no mention anywhere in Section 1 of	Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD. Comments noted.

Consultee	Comment	Response
	the potential for substantial savings by preventing usage of EGFR antagonists in patients with mutRAS or wtEGFR. Targeted use of gefitinib in the first line setting will largely eliminate the use of erlotinib in the second line setting. This shift in clinical practice carries with it a significant potential cost-saving. It isn't clear how NICE have taken this into consideration in their evaluation. The document also repeatedly mentions the cost related to biopsy and suggests that repeated biopsies may be needed. However, our understanding is that, in actual clinical practice, the biopsy used to make the first diagnosis is usually suitable for EGFR analysis. <u>The role of NICE in appraising stratified medicines:</u> In this and in future appraisals we feel it is crucial that NICE exploits the best science available. We recognise that in the Appraisal Consultation Document, NICE has asked the manufacturers to address some clarifying questions. We also ask that NICE seek additional oncological expertise in answering some of these questions. For example, we believe that the establishment of an EGFR-TK mutation testing service would not be as complex as suggested in the appraisal (point 3.27) and that this is something the manufacturers would likely be inclined to support. Furthermore we are concerned that NICE has overestimated the likely lifetime for patients with locally advanced or metastatic disease (point 3.32) in this appraisal. We hope that NICE will work quickly to resolve these issues. It is already nearly six months since gefitinib was launched for use as a first line treatment for non-small cell lung cancer in the UK, and many patients who could benefit from this treatment are being left in limbo while this decision is being made. We urge NICE not to miss this golden opportunity to support the development of stratified medicines and recommend the use of targeted treatments for cancer patients in the NHS.	Costs related to biopsy and the possible need for repeat biopsy are not included in the FAD. Section 4.3 of the FAD states that the Committee was persuaded that testing for the EGFR-TK mutation would not limit treatment and that it should be seen as analogous to testing for human epidermal growth factor receptor 2 (HER2), which has been successfully implemented in a short timeframe within the NHS. Comments noted
Royal College of Physicians	• Page 15 - 3.24 Cisplatin and Vinorelbine are not commonly used in the U.K. for the treatment of advanced or metastatic lung cancer. • Page 16 - 3.28; The statement about blinding is not strictly accurate. Evaluation of CT scans etc was blinded within the treating centre but it is true there was no independent review of scans.	Section 4.2 of the FAD outlines that the principal treatments used in UK clinical practice tend to be gemcitabine with cisplatin or carboplatin and, increasingly, pemetrexed plus cisplatin. Comments noted

Consultee	Comment	Response
	• Page 17 - 3.29 There is as yet no evidence of an interaction between EGFR mutation status and chemotherapy sensitivity. If one looks at the EGFR M-ve patients in the IPASS study who received chemotherapy and compares it with the patients who had wild type chemotherapy the median progression free survival of the 2 groups are very similar. • Page 24 - 4.5 the identification of progressing patients was blinded • Page 26 - 4.9 there is a major problem with the inclusion of cisplatin/pemetrexed in the mixed treatment group and indeed of any other survival data derived from non-Asian sources because in the IPASS study the majority of patients were female and in the Scagliotti, the majority of patients were male. Sex is known to be an important determinant of survival in NSCLC with women surviving longer. Economic Model: The major criticism of the economic model is that no account has been taken of the effect of EGFR mutation testing and first line use of gefitinib will have on second line receptor tyrosine kinase inhibitor use. It will almost certainly fall very substantially resulting in large cost savings	Comments noted. Comment noted. Please see section 4.4 of the FAD. Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.
Royal College of Pathologists	These comments relate only to points raised that are relevant to the role of the pathologist in testing for the EGFR mutation(s) that would inform treatment options: <u>EGFR mutation testing:</u> The last year has seen this test being increasingly requested, with data from varying UK groups suggesting that mutations are identified in 10-15% of cases diagnosed as adenocarcinoma. The instigation of a process for sending material from diagnostic pathology laboratories to molecular units has proved relatively straightforward, with a low failure rate in relation to the test (although techniques vary between centres) itself. If anything, the main issue relates to the volume of tumour cells required with a 'failure rate' in terms of tumour volume of around 10% in our experience. However, recent publications state that mutations are identifiable even in fine-needle aspirations (e.g. Garcia-Olivie et al. Eur Resp J 2010;35:391) and our College is addressing these issues in relation to its "Tissue Pathways for Lung Disease" document, which is currently being updated to account not just for implementing mechanisms that allow tissue to be saved for potential mutation testing but also for the refinement of the diagnosis of non-small cell lung carcinoma	Comments noted. Please see FAD sections 4.3, 4.7, and 4.16.

Consultee	Comment	Response
	(NSCLC) to either squamous cell carcinoma or adenocarcinoma, whenever possible. As clinicians and pathologists become more aware of the potential need for testing, the 'tumour volume' issue may lessen as the type of sample required may be planned accordingly as part of multidisciplinary review. The cost for a mutation test is around £150 at present but will come down with increasing volume. There is also research ongoing into immunohistochemical assessment of mutations which may bring the cost down further, although this may be a while into the future. <u>Population for testing:</u> The amount of testing could be further refined by limiting it those cases that are adenocarcinoma, either morphologically or via immunohistochemistry, which is already part of the diagnostic process in many UK laboratories in relation to NSCLC. However, there is an argument for the group for testing to be those that are 'non-squamous' as the NSCLC population will contain some adenocarcinomas, albeit more poorly differentiated and with a likely lower mutation rate (although this is unproven on biopsies). At present, there are insufficient data to argue convincingly for testing just "adenocarcinomas" or a larger "non-squamous NSCLC" group. However, the RCPath "Tissue Pathways" updated document intends to make it part of the process to refine NSCLC whenever possible, which may reduce the problem by identifying more cases with an adenocarcinoma immunohistochemistry profile. This subgroup is not a group that have been validated in relation to mutation status etc., but it would be reasonable to test such cases in patients who were being considered for targeted treatment.	
Roy Castle Lung Foundation	This letter is a response, on behalf of the Roy Castle Lung Cancer Foundation. We are extremely disappointed that, despite the expert testimony of key lung cancer professionals during the Appraisal Committee Meeting, the recently issued ACD on the use of Gefitinib in the first line treatment of non-small cell lung cancer, reveals that the Committee is minded not to recommend this therapy. This therapy represents a targeted treatment option, providing benefit to a clearly	Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.

Consultee	Comment	Response
	defined segment of non small cell lung cancer patients. It is an oral medication and, in the anecdotal patient experience reported to us, is very well tolerated. We would wish to remind the Committee of the overall poor prognosis and low survival rates for this patient group. Even relatively small improvements in survival and quality of life, as compared with the current established therapy, are of real importance to patients. We hope that, during its deliberations, the Appraisal Committee will be mindful of this and take it in to account. We do note the Appraisal Committee's request to the manufacturer for further clarification and cost-effectiveness analyses. After consideration of this, we strongly urge the Committee to issue a positive FAD for this therapy indication.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None		

Comments received from commentators

Commentator	Comment	Response
Lilly	We welcome the opportunity to review and comment on the appraisal consultation document (ACD) for gefitinib in first-line NSCLC. Lilly believe that the summaries of clinical and cost effectiveness in the ACD appear to be reasonable in the light of the available clinical evidence. However, we have some con-cerns relating mainly to the methodology of the mixed treatment comparison (MTC) and the economic analysis, which are described below. MTC incorporates hazard ratios from different patient sub-groups for different comparators: We acknowledge the difficulties of providing suitable evidence versus comparators com-monly used in UK clinical practice with an indirect comparison methodology. This meth-odology requires that the studies selected for such comparison address similar patient populations to ensure robustness of results. To that end, we are concerned that the manufacturer's submission uses efficacy data for the non-	Comments noted The Committee accepted that there was uncertainty in these comparisons but it concluded that it was likely that gefitinib was no less efficacious than pemetrexed and cisplatin, and that pemetrexed in combination with cisplatin was the relevant

Commentator	Comment	Response
	squamous subgroup of patients for pemetrexed/cisplatin, when the efficacy data for all the other comparators in the net-work are for patients with all NSCLC histologies. Lilly believe that a separate indirect comparison between pemetrexed/cisplatin and gefitinib would allow a more robust evaluation of their comparative efficacy in more specific histology subgroups.	comparator for gefitinib. See FAD section 4.9.
	Use of progression-free survival and immature overall survival data in the eco-nomic model:	
	Data from IPASS has shown that gefitinib improves progression-free-survival (PFS) compared to paclitaxel/carboplatin. The data on PFS are the basis of the economic model in the manufacturer's submission. Whilst we think PFS is important because it allows to assess the direct effect of the drug without the confounding effect of subsequent therapy, from an economic point of view it has some disadvantages since PFS in itself does not provide the evidence on extensions of length of life that is required for the estimation of QALYs gained from treatment.	Comments noted. Please see FAD section 4.13.
	The economic analysis should ideally incorporate more mature OS data from the IPASS trial. While it is reasonable to use immature OS data in the absence of final OS data, we would like to ensure that additional assumptions are explored in the projection of OS data to characterise the uncertainty this may have on the ICER estimates. In the absence of additional clinical trial data establishing the OS benefit for gefitinib in any other NSCLC setting, it is essential that other methods to model OS are fully explored in order to in-crease the level of confidence in the ICERs.	
	Additional concerns regarding the economic model:	
	• The results of the MTC for pemetrexed in terms of safety appear to be inconsistent with its known tolerability profile, i.e., the risk of anaemia, fatigue and nau-sea/vomiting appear to be unduly high for pemetrexed/cisplatin compared to pacli-taxel/carboplatin.	Comments noted
	• The same rate of G-CSF use (22%) has been applied across all regimens. We believe that it would be more appropriate to apply a differential rate based on the probability of neutropaenic events with each regimen. For example, in the phase III trial comparing pemetrexed/cisplatin with gemcitabine/cisplatin in first-line NSCLC (Scagliotti et al, J Clin Oncol 2008) G-CSF was used in only 3.1% of patients in the pemetrexed/cisplatin arm and 6.1% of patients in the gemcitabine/cisplatin arm. Furthermore, the cost of G-CSF assumes that all patients would receive the	

Commentator	Comment	Response
	maximum duration of 14 days. The model should therefore reflect current UK practice in terms of treatment duration for G-CSF, which would then be explored in the sensitivity analyses. • Due to limitations in reported data, alopecia was not included in the MTC. However, the assumption of an equivalent rate across all non-gefitinb regimens is unlikely to be valid. Though alopecia does not carry cost implications in the economic model, it has a relevant impact on utility values. Choice of comparators to gefitinib: Omission of pemetrexed/cisplatin as comparator in the original submission Subsequent to the publication of NICE guidance (TA181) recommending pe-metrexed/cisplatin in first-line NSCLC, this regimen is increasingly accepted as one of the main treatment options for patients with adenocarcinoma and large cell carcinoma in Eng-land and Wales. According to the marketing authorisation for gefitinib and the manufacturer's submission to NICE, the target population for gefitinib appears to be the subgroup of patients with adenocarcinoma and EGFR-TKI positive mutations. Since most adenocarcinoma patients in the NHS currently are eligible to receive pemetrexed/cisplatin, it is the most suitable comparator to gefitinib in this subgroup of patients. We are therefore pleased that the appraisal committee have requested additional analyses comparing gefitinib with pe-metrexed/cisplatin. Efficacy of gemcitabine/ cisplatin in advanced NSCLC compared to other platinum doublets: Prior to the introduction of pemetrexed, gemcitabine in combination with cisplatin or car-boplatin has been widely accepted in UK clinical practice as the gold standard for first-line NSCLC patients, irrespective of tumour histology. Results of a meta-analysis by Le Chevalier et al. (2005), suggested that the gemcitabine/cisplatin doublet had a significant benefit over other platinum doublets. Therefore, we question the appropriateness of paclitaxel/carboplatin as the comparator of choice in the IPASS clinical trial as there is evidence suggesting that clinical benefits of paclitaxel/carboplatin are surpassed by another platinum doublet in use at the time.	Comments noted The Committee accepted that current standard practice in England and Wales until recently was gemcitabine with a platinum drug, but that pemetrexed plus cisplatin is increasingly used. The Committee concluded that in UK clinical practice pemetrexed plus cisplatin is the most appropriate principle comparator for gefitinib.

Commentator	Comment	Response
	In view of the fact that gemcitabine/platinum is still the most widely used chemotherapy doublet in patients not eligible for pemetrexed/cisplatin, Lilly agree with the ERG's comments that the First-SIGNAL trial comparing gefitinib to gemcitabine/cisplatin should have been included in the meta-analysis of gefitinib trials. Transferability of IPASS efficacy outcomes to UK clinical practice: The main evidence used in the manufacturer's submission was based on IPASS, a trial that recruited patients exclusively from Asia. As stated in the European Assessment Re-port (EPAR) for gefitinib, data from a pooled analysis from clinical trials and the literature show that in EGFR M+ tumours there is a higher response rate in Asians than in non-Asian. In addition, EGFR mutations occur more frequently in Asians than non Asians (40% vs 10%) and therefore these higher rates translate into better efficacy with gefitinib. The manufacturer has committed to providing new evidence to the EMA on the efficacy of gefinitinib in a Caucasian population. Until that evidence is available, due consideration should be given to the uncertainty around efficacy outcomes and the corresponding trans-ferability of such outcomes to the UK clinical practice.	Comment noted The Committee considered how the evidence from IPASS related to the target population of EGFR-TK mutation-positive patients with locally advanced or metastatic NSCLC treated in England and Wales. The Committee accepted advice from the clinical specialists that the efficacy of gefitinib depended on EGFR-TK mutation status and that there was no reason to assume that efficacy differed according to gender, ethnicity, histological subtype or smoking status. See section 4.4 of the FAD.
British Thoracic Oncology Group	The following comments are made on behalf of the British Thoracic Oncology Group (BTOG) with regard to the NICE ACD 'gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer' issued January 2010. The organisation would like to express its disappointment that NICE was not minded to recommend gefitinib for the appraised indication. In rapidly moving fields where clinical trials of drugs with novel mechanisms of action are under development it is always possible for more research to be undertaken or for existing data to become more mature. The problems are multiplied	Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.

Commentator	Comment	Response
	when the new treatment is targeted at a new genetically defined disease such as activating mutations of EGFR which essentially define a previously unknown disease entity. Thus an analysis of survival of NSCLC patients with activating mutations of EGFR before and after introduction of gefitinib showed a doubling of median survival in these patients, but no change in mutation negative patients (Takano et al, J Clin Oncol, 2009). This situation hasn't arisen since mutations in c-kit defined most gastrointestinal tumours (GISTs) as a disease definable by sensitivity to imatanib. It is easy to retreat into the cul du sac of claiming more data is needed but not very sympathetic to a rapidly evolving field. In these situations the addition of the novel therapy adds to standard treatments in terms of PFS and survival. The question of 'comparator' is not so easy to define. In the available data the chemotherapy comparator was chemotherapy with carboplatin and taxol. This chemotherapy is widely used in the USA, often for 6 cycles or even until disease progression. In Europe and the UK first line treatment has generally not included a taxane and we tend to favour cisplatin over carboplatin because of the meta analysis superiority of cisplatin over carboplatin. Most patients with EGFR mutations (> 95%) are non-squamous cancers thus the UK/European comparator would be cispaltin 75 mg/m2 plus pemetrexed 500 mg/m2 given for up to 6 cycles with a median of probably 4-5. This chemotherapy is well tolerated with a febrile neutropaenia rate of 1.4%. Other regimens such as cisplatin/navelbine have such high febrile neutropaenia rates (around 10-17%) that clinicians rarely use them and are no longer real world comparators. Thus the most realistic comparator for gefitinib first line would be cisplatin/pemetrexed. It is of interest that NICE in point 1.5 comment about the shape of the survival curves and exploration of alternative probability distributions. I am sure that the provision of patient level data will resolve this red herring and it is very unlikely that Weibull distribution curve will be statistically bettered. As ever the very blunt quality of life assessments made by NICE undermine the real quality of life benefits for patients who receive gefitinib first line. The Expert Review Group seems to have been confused about these points. Thus in 4:13 (page 30 of 47) they analyse the data by inappropriate measures such as hazard ratios so as cross study comparisons could be made. It is a constant disappointment to clinicians that the diligent collection of quality of life (QoL) data is not fully taken into account by NICE who rely of generic QoL tools such as EQ5D, rather than validated disease	.

Commentator	Comment	Response
	specific models. We would urge NICE to take account of the large benefit which gefitinib brings to patients with activating mutations of EGFR in the first line setting. These patients have significantly increased objective tumour response rates and prolonged progression free survival if they receive gefitinib first line. These observations correlate with improved disease specific symptom control. We accept that overall survival has not yet been convincingly demonstrated in a randomised controlled trial but are optimistic that in the near future additional information will be available from clinical trials to make the case for first line gefitinib in this indication overwhelming. This is underpinned by the data of Takano et al discussed earlier which indicate that when a large benefit is associated with any given treatment it is clinically obvious.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	3	Technical test failure is predicated on many factors related to laboratory practice and to what extent testing will be attempted on the very smallest samples. There is no recognised standard our technical test failure rate is about 6%. False negative tests are a risk of testing inadequate samples. False positive tests are much less likely artefacts can be check detected, contamination should be avoided by Good Clinical Laboratory Practice measures.	Comments noted

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 1	4	Regarding the issue of (likely) prevalence of EGFR mutations in a UK population, the disparity in figures reflects the substantial differences in the denominator in the equation i.e. the population of cases actually tested. Published data vary enormously from less than 5% to around 20% of European or caucasian cohorts. Sample type, testing methodology employed and case selection all influence the chance of finding a mutation. In caucasians, EGFR mutation is extremely unlikely is squamous cell carcinoma (SCC). SCC accounts for perhaps 40-45% of UK NSCLC. By including these cases in a tested population, the prevalence of mutations is diluted. This is one reason for the figures circa 5% quoted by some. Our local experience of some 80 or so cases tested is that EGFR mutation is found in approximately 18% of tested cases. This will reflect an exclusion of squamous cell carcinomas but also some positive selection of patients with a higher chance of mutation. I believe in a non-squamous NSCLC population tested in the UK the prevalence is likely to be somewhere between 10-15% of cases. There may well be differences within the UK.	The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be between 10% to and 15% in the target population. Please see FAD section 4.16.

Role*	Section	Comment	Response
NHS Professional 2	1	The following is the experience of the Royal Marsden NHS Foundation Trust in routine EGFR genotyping in lung cancer patients (mainly NSCLC but not exclusively, first and second line, adenocarcinomas + squamous) since May 2009 until January 2010. Please note that due to the heterogeneity of the population studied, these data do not reflect the real prevalence of EGFR mutations in "NSCLC Adenocarcinoa subtype": EGFR genotypes Â 228 EGFR mutations Â 27 Failures due to insuficient material, lack of amplifiable DNA or technical issues Â 26 (11%) Total percentage EGFR mutants(not consiering failed samples) Â 13% Percentage of female patients tested: 54% Percentage of EGFR mutations in female patients v male patients Â 12% v 8% (this include failed samples, hence percentages 13%) The price per test based on our current workload (10 samples/week) and including consumables, reagents, instrument maintenance, staff costs, etc... ranges from Â£200 for the DxS technology to Â£125-Â£150 for the others. If the number of samples/week was 5, the cost of these tests will increase by approximately 15-25%.	The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be betweenapproximate 10% to and 15% in the target population. Please see FAD section 4.16. Comment noted. Please see FAD section 4.16.
NHS Professional 2	3	We have used different methods, ranging from the ARMS-PCR kit (DxS) to ASO-PCR, Fragment analysis and sequencing. In our hands, all methods had a similar sensitivity apart from sequencing, where the sensitivity is significantly lower. In our experience, the risks of identifying EGFR mutations in samples that carry no mutations (i.e. a false positive result) are ver low, specially for the well-characterised mutations (i.e. exon 19del, L858R, exon 20dup). However, the risk of missing EGFR mutations (i.e. false negative cases) is more likely to occur, due to the heterogeneity of the tissue samples and methods used.	Comments noted

Role*	Section	Comment	Response
NHS Professional 2	4	We have studied a wide range of different samples, from core lung biopsie to cytological specimens, such as TBNA, FNA, EBUS, etc... We have found the EGFR genotyping is feasible in most samples, including small biopsies and cytological specimens. This has been published in J Thorac Oncol. 2010 Jan 8. [Epub ahead of print]	Comments noted
NHS Professional 3	4	4.3 EGFR mutation testing is available within South Wales. 4.16 For lung cancer patients, the potential quality of life issues related to fewer hospital stays and lengthy visits are perhaps not fully appreciated when measuring specifically health-related quality of life. The expectation of treatment for many lung cancer patients at diagnosis are: good symptom control, an improvement in prognosis, a proactive approach by the team caring for them and minimal disruption to their life allowing them to do as much as possible with the time they have left. The reduced need for hospitalisation impacts positively on the patient and carers, particularly when Oncological treatment and management of side effects thereafter is routinely provided in a Centre many miles away from home. The side effect profile for Gefitinib are more manageable in the outpatient setting than those associated with the platinum based doublet that is the Â current standard of care.Through an improvement in quality of life patients are able to better manage their end of life issues and focus on their personal priorities with greater control.	Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD. The incorporation of benefits to health-related quality of life and utility in the manufacturer's economic model are discussed in section 4.12 of the FAD.

Role*	Section	Comment	Response
NHS Professional 4	4	Molecular analysis of EGFR mutations has been established as a diagnostic service during the last 6 months in several NHS Regional Genetics Labs (Cardiff, Aberdeen, Exeter, Sheffield and Manchester). 249 EGFR tests have now been performed by Regional Genetics labs using DNA sequencing, Pyrosequencing and fragment length analysis. Technologies are designed and validated to detect 98% of published EGFR activating mutations. Mutations are detected with sensitivity of 3-6% (Pyrosequencing) and 10-20% (Sequencing) in an admixture of tumour and normal cell DNA. Results are qualitative, a mutation is either detected or not. 33 (18 male / 15 female) EGFR mutations have been detected in 249 (133 male / 166 female) patient samples (13%). Analysing laboratories do not always have access to tumour histology information. Many of the 249 samples analysed were adenocarcinomas, but a significant number of samples were squamous, large cell or not stated. 166 (46.6%) of the 249 samples were taken from female patients, the ethnicity of patients is generally unknown. The cost of a single EGFR analysis is generally accepted to be approximately Â£200.	The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be between 10% to and 15% in the target population. Please see FAD section 4.16. The likely volume of tests that would be carried out, and the cost of testing is discussed in section 4.16 of the FAD.

Role*	Section	Comment	Response
NHS Professional 5	1	re: 1.10 evidence of mutation frequencing in the UK population is being generated from a number of clinical laboratories in the UK who have been providing an EGFR testing service over the past few months (Manchester 7/67 Â 10.5%) Selection of patients with NSCLC for EGFR testing is appropriate Â based on histopathology There is no compelling evidence that EGFR mutations are present in squamous NSCLC See Marchetti A, Martella C, Felicioni L, Barassi F, Salvatore S, Chella A, Camplese PP, Iarussi T, Mucilli F, Mezzetti A, Cuccurullo F, Sacco R, Buttitta F. J Clin Oncol. 2005 Feb 123(4):857-65. ? series of 454 squamous NSCLC no EGFR mutations detected This study had good histological review to confirm tumour type Selection of patients guided by histological subtype is likely to result in much higher yield of positive EGFR mutation results Screening patients with no likelihood of mutation will have an effect on laboratory work load potentially impacting on turnaround time and would generate costs to the health service with no likelihood of influencing treatment decisions. Testing in all other subtypes of NSCLC would be appropriate.	The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be betweenapproximate 10% to and 15% in the target population. Please see FAD section 4.16. Comment noted. Please see FAD section 4.19

Role*	Section	Comment	Response
NHS Professional 5	2	re 2.2 Many clinical laboratories are providing EGFR testing within the UK to support oncology practice. External Quality Assessment for EGFR testing will be introduced in these accredited labs in line with other genetic tests. This QA process will ensure the accuracy and sensitivity of the techniques used by the laboratories. Therefore we do not think that a specific type of genetic test for EGFR analysis should be recommended but that different laboratories should employ the test that they can validate and that provides robust coverage of the common EGFR mutations in exons 18-21. Future advances in genetic analysis will mean that different technologies (specifically high throughput DNA sequencing) will be appropriate to provide an EGFR mutation testing service in the next few years Mutation testing is generally successful on tumour tissue samples (1 fail in 68) We have had success in identifying mutations in cytology samples transferred into a paraffin block For this reason we do not believe that microdissection of samples is mandatory. However we do believe that close liaison between histopathologists/cytopathologists and geneticists is vital to provide the optimum service	Comments noted
NHS Professional 5	3	RE 3.31: The current costs for EGFR testing ~Â£200 per test are unlikely to reduce in the short term. Increased volume of samples will not reduce the unit cost as most costs relate to the analysis and interpretation of the genetic testing and generation of a clinical report	Comments noted. Please see FAD section 4.16.
NHS Professional 5	4	re 4.3 Many clinical genetics/pathology laboratories are providing EGFR testing within the UK to direct appropriate prescription. Provision is increasingly available and we have disseminated our service profile to relevant physicians throughout the North West	Comment noted

Role*	Section	Comment	Response
NHS Professional 6	1	Section 1: In Birmingham Dr Taniere and I have been routinely performing EGFR mutation testing in an NHS facility since May 2009. Â Samples from 185 cases of NSCLC have been submitted. We were able to test successfully 175 without resorting to rebiopsy. Â Activating mutations on exons 19 and 21 were found in 21 (12%). Â The histology of submitted samples was adenocarcinoma/BAC 119, squamous carcinoma 6, adenosquamous carcinomas 2, NSCLC not otherwise specified 46, others 2. Â About 66% of our cases of NSCLC are non-squamous so this approximates to an overall mutation frequency of ~8%. We believe it is unnecessary to routinely test patients with squamous carcinoma because the pickup rate is 1%. In 13 cases we had both histology and cytology specimens and in all these there was concordance, including 2 cases with mutations. Having treated 6 cases of mutation positive disease with either gefitinib or erlotinib since January 2010, I (MHC) am impressed by the response rate (5/6, 83%) which matches published data in SE Asians, and by the excellent tolerance to, and quality of life associated with gefitinib.	The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be betweenapproximate 10% to and 15% in the target population. Please see FAD section 4.16.
NHS Professional 6	4	Since virtually all activating mutation positive cases are adenocarcinoma, gefitinib would replace our current standard therapy for adenocarcinoma which is cisplatin plus pemetrexed. Â Our current second-line therapy for appropriate cases of adenocarcinoma is erlotinib. Â If gefitinib was approved then erlotinib would not be used for any mutation positive cases.	Comment noted.
NHS Professional 7	1	This is a very disappointing development for NSCLC patients in the UK. The current option for fit patients is to undergo a course of chemotherapy which carries significant toxicity. I have experience of giving gefitinib within the expanded access programme and this is a much better tolerated drug. We often see audits presented at British Thoracic Oncology Group Annual Meetings showing the first line chemotherapy is associated with a significant rate of admission to an inpatient facility. In my experience about 20% of patients having chemo for NSCLC will end up being admitted either for neutropenic of non neutropenic sepsis. This is a major cost burden on the NHS. Gefitinib causes a minimal degree of myelosuppression. Additionally the oral nature keeps patients away from overburdened chemotherapy units. The impressive quality of life benefits of gefitinib over chemotherapy shown in IPASS need to be given more consideration.	Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.

Role*	Section	Comment	Response
NHS Professional 7	2	The single payment access scheme is interesting. From clinical experience we know that about 10% of patients may remain on this drug for quite long periods of time. While the median OS from IPASS is impressive, extrapolating from BR21 erlotinib data, small numbers of patients could be on this drug for years. There are tens of thousands of British subjects of East Asian origin who reside and pay taxes in the UK. For them I would say denial of gefitinib is potentially discriminatory as many of these patients are predisposed to having an EGFR mutation. While the benefits of gefitinib are driven by mutation, it is fair to say that Western and Asians both benefit however, the mutation is more prevalent per se in Asian patients. The cost/benefit analysis for this subgroup would therefore be totally different.	Comments noted Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.
NHS Professional 7	3	The important thing here is the comparator chemotherapy regimen. For a fit patient with adenocarcinoma the standard treatment is cisplatin and pemetrexed. This is in line with NICE guidance. Patients usually recieive 4-6 cycles of therapy. In my experience about 80% will stop at 4 cycles but 20% complete 6 cycles. You need to consider all 4 randomised trials of gefitinib in EGFR mutated NSCLC. IPASS and First signal were in clinically selected groups. NEJ002 and WJTOG3405 were in EGFR mutated patients. The latter 2 may be more relevant even though IPASS is the largest study. The holy grail on oncology research has been to find the tests that predict who will benefit from specific treatments. The IPASS trial now defines a new subtype of NSCLC called EGFR mutated NSCLC. You really need to think of this as a new disease with a different treatment paradigm. Continuing to think of this as regular lung cancer is blinkered and unhelpful.	Comments noted.

Role*	Section	Comment	Response
NHS Professional 7	4	As an oncologist I would say the main benefit of treatment with metastatic disease is to palliate symptoms and help patients maintain their quality of life. Improvements in PFS and OS are welcome additions. The standard comparator should be cisplatin and pemetrexed. IPASS clearly shows that EGFR mutation is the key driver of benefit. The criteria for trial entry were designed to enrich for EGFR mutation. The prevalence of EGFR mutations in lung cancer have never been properly assessed within the UK population. Based on the unpublished data I have seen it is between 10-20%. There are massive quality control issues with regards to the amounts of tissue obtained during the diagnostic process. Often the test fails due to lack of viable tumour cells. Now that histology is important determining which chemotherapy drugs we use (pemetrexed for adenocarcinoma) I predict that there will be a gradual move to obtain formal tissue. Cytology is increasingly being frowned upon. With more biopsies, there will be more tissue to do molecular testing. It is likely that we will see the incidence of EGFR mutation rise to 15-20%. This is assuming the testing is performed in adenocarcinomas.	Comments noted. Please see FAD section 4.9, The Committee agreed that pemetrexed in combination with cisplatin was the relevant comparator for gefitinib. Comment noted The Committee heard from the clinical specialists that the prevalence of EGFR-TK -positive mutations in patients with NSCLC may range from 5.0% to 17.0% depending upon the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. The Committee was therefore satisfied that the prevalence of the EGFR-TK -positive mutation was likely to be betweenapproximate 10% to and 15% in the target population. Please see FAD section 4.16.

Role*	Section	Comment	Response
NHS Professional 7	7	Mature overall survival data for some of the trials may become available shortly after NICE guidance is out. It would be very unfortunate if NICE then took a few years to reassess the data. This would deny thousands of patients a potentially effective drug. It took years for erlotinib to get approved in the UK and it would be a real pity if the same happened here. I would be very keen to see an early reassesment if survival data became available shortly after NICE guidance.	Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.
NHS Professional 8	1	It is not clear whether the economic appraisal includes the impact of testing all NSCLC patients, excluding those with proven squamous cell carcinoma or carcinoid, on the provision of services to lung cancer patients at Cancer Centres. Patients on gefitinib will be treated at home with outpatient/GP appointments, in comparison with the alternative of chemotherapy with more frequent visits and likely requirements for hospitalisation. This will reduce pressure on oncology facilities and their provision. Â Have these potential cost savings been taken into account?	Please see FAD section 4.19 which notes that the Committee accepted the views of the clinical specialists that testing should be carried out on all patients irrespective of gender, ethnicity, and smoking status to ensure that all patients who could benefit would be identified.
NHS Professional 8	3	There seems to be an erroneous view that EGFR-TK mutation testing is not available within the NHS. Â Ten centres within the UK have already signed up to National External Quality Assurance Scheme for testing, and around 10 others are at various stages of start-up. It should be feasible for all NSCLC patients (excluding SCC and carcinoid) in England to have a test within months rather than years of any decision to implement a blanket testing protocol, which is likely to be less expensive and more effective than any alternative. Â A comparison with the introduction of HER2 testing would be apposite.	Section 4.3 of the FAD notes that the Committee was persuaded that testing for the EGFR-TK mutation would not limit treatment and that it should be seen as analogous to testing for human epidermal growth factor receptor 2 (HER2), which has been successfully implemented in a short timeframe within the NHS.
NHS Professional 8	4	The cost of testing using ARMS technology is currently around Â£100 per patient excluding staff costs. It should be feasible to reduce this very substantially using alternative technologies. Â In addition, automation and the use of plasma for testing, particularly in those patients without sufficient biopsy material, are highly likely to be able to reduce the costs of testing further within the next year. UK prevalence data for EGFR-TK mutations will be derived from the manufacturer-funded testing centres in due course.	Comments noted.

Role*	Section	Comment	Response
NHS Professional 8	7	This is a rapidly developing field. In my opinion this advice should be reviewed one year after issue.	Comment noted
NHS Professional 9	3	The ICER figures quoted in 3.37 seem implausible. Â The ERG states that the ICER even in their re-analysis is 38,000 per QALY gained cf carboplatin/paclitaxel. Â I find it unlikely that this figure is more than doubled by changing chemotherapy to pemetrexed/cisplatin, given the very modest advantage of pemetrexed/cisplatin over other standard chemotherapy regimens discussed in TA181. Â The methodology used by the ERG needs to be examined closely.	Comment noted
NHS Professional 9	4	My strong opinion is that it is the ERGs figures which seem implausible, not the manufacturers, and the Committee seems to feel the same. Â It seems perverse therefore to use this as a basis for not recommending this treatment. It also seems very clear that the committee is underestimating the QoL advantage of oral outpatient therapy with gefitinib compared to combination chemotherapy which is in my experience very significant and is strongly supported by the evidence. Â Again it seems perverse effectively to ignore this. Â Would the committee take the same view and ignore the QoL data if it was worse with the technology under evaluation? I would ask the committee to reconsider this opinion which is in my view not supported by the evidence presented	Comments noted. Gefitinib is now recommended when specific criteria are met. See section 1 of the FAD.