NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive 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
British Thoracic Society	Thank you for sending this excellent piece of work. The answers to your questions are given below within the original text of your email. I am concerned that the issues of the ethnic difference in the study populations for gefitnib and erlotinib have been inadequately considered by both the manufacturer and the ERG. Have you considered the potential benefits of erlotinib, where the study population is much closer to the UK population? Have you also considered that the frequency of the EGFR mutation is relatively low in the UK? Racial issues: gefitinib is clearly effective in improving PFS in East Asians but the evidence in other ethnic groups is really only for erlotinib, so by approving one and not the other you could risk disadvantaging the majority with EGFR mutation in the UK. I agree that there needs to be a more equitable cost differential and would support the further questions, but with the wish that erlotinib is approved as an alternative first line therapy for these patients who have a most appalling prognosis. • **Has all of the relevant evidence been taken into account**? Yes • **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** See comments above • **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** Yes • **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** Probably	Comment noted. The Committee considered that the evidence from the EURTAC trial was relevant to the UK population, however the Committee did not consider an indirect comparison between the treatments was appropriate because of differences in the trials. The Committee requested an updated model based on an assumption of equal efficacy between erlotinib and gefitinib in the progression-free state. The Committee considered the results from the updated model and concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC. No equalities issues were identified by the Committee and the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups and that there was no need to alter or add to its recommendations because of NICE's duties under equalities legislation.

Consultee	Comment	Response
Department of Health	The Department of Health has no substantive comments to make regarding this consultation.	Comment noted.
Joint response from NCRI, Royal College of Physicians, RCR, ACP, JCCO	We are grateful for the opportunity to respond to the above ACD consultation and would like to make the following comments. Our experts are disappointed to learn that NICE is minded not to approve erlotinib for this indication. They are satisfied that the committee has considered erlotinib and gefitinib relatively comparable in terms of efficacy and toxicity, this conclusion therefore being contingent on a health economic model. The ERG model has been based on 76% of gefitinib patients incurring the fixed cost of gefitinib. In current clinical practice the feedback received is that this rate is considerably higher; indeed potentially above 90% at some centres We would therefore ask NICE to reconsider its decision to take account of this information.	Comment noted. The Committee discussed the results from the updated analyses where gefitinib and gefitinib have equal efficacy and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.
NHS Derby City	**Response to appraisal consultation document** 1. Has all of the relevant evidence been taken into account? 1st line treatment in UK for EGFR-TK mutation in positive NSCLC is gefitinib. Data presented by the manufacturer do not present head to head comparison of gefitinib with erlotinib but indirect evidence. Although the data presented show superiority in terms of efficacy of erlotinib over standard chemotherapy, there is no data comparing it to other possible treatment options. Due to the fact that there were no head-to-head trials with gefitinib (currently first line treatment), it remains to be seen what advantage erlotinib has over gefitinib. 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The manufacturer's estimated 0.76 per 100,000 population for treatment with first-line erlotinib. Other estimates have suggested eligibility up to 5 people per 100,000. Clarity should be sort with regards to the eligible population.	Comment noted. The updated model presented by the manufacturer in response to the appraisal consultation document incorporated identical utility values for patients receiving erlotinib and patients receiving gefitinib in the progression-free survival health state. The Committee discussed the results from the updated analyses and it concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

Consultee	Comment	Response
	An ICER comparing the costs with gefitinib is needed to assess the cost-effectiveness. The committee did not have sufficient information to assess the most plausible ICER for erlotinib compared to gefitinib. Clinically erlotinib is more effective than standard chemotherapy but we do not know if it is more or less effective in comparison to gefitinib. 3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? CSAS reply to NICE concerning ACD for erlotinib appear sound. They have highlighted relevant concerns from the ACD. There are no details regarding the Patient Access Scheme in the document, stating the information is commercial in confidence. As commissioners it would be helpful to understand the practical details involved in this PAS. The current PAS for gefitinib has proved to be relatively complicated to manage. We would request that this PAS should be straightforward to administer. 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None identified 5. Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document? None identified	

Consultee	Comment	Response
Roche	*Roche submitted the additional analyses as requested by the Committee. Comments included in their response are:* **The assumption that erlotinib and gefitinib are associated with equal time in PFS** We acknowledge the difficulty in assessing the cost-effectiveness of erlotinib relative to gefitinib (primarily due to the lack of evidence on the efficacy of gefitinib in Caucasian patients and the complexity of the gefitinib patient access scheme); however the assumption that erlotinib and gefitinib are associated with equal time in PFS appears unnecessarily pessimistic towards erlotinib. The evidence base available indicates that whilst the two treatments may be *similar*, erlotinib is likely to be modestly more effective than gefitinib. Whilst the above analyses demonstrate that approval of erlotinib is a cost-effective use of NHS resources even if it is assumed that erlotinib and gefitinib are associated with equal time in PFS, we believe this assumption is not reflective of the evidence available. *A comparison of erlotinib and gefitinib in comparable patient populations* Whilst a comparison of erlotinib and gefitinib based upon the EURTAC study is subject to clear heterogeneity between the European EURTAC study and the East Asian gefitinib RCTs (an issue raised in the ACD), this is not the case for a comparison of East Asian OPTIMAL and the gefitinib RCTs. Each of these studies were broadly comparable (to the extent that the IPASS and OPTIMAL RCTs were conducted in largely the same centres).	Comment noted. The Committee considered the evidence in the manufacturer's submission and concluded that there was insufficient evidence to support the difference in clinical effectiveness between erlotinib and gefitinib in the original model. The Committee requested an updated model based on there being no difference in the clinical benefit between the treatments. The Committee was aware of the limitations of this type of economic model which incorporates no uncertainties about survival. The Committee concluded that the updated economic model was in line with clinical opinion and reflected the absence of any clinical data from direct comparisons, and so allowed a direct comparison of the costs of the two treatments.

Consultee	Comment	Response
	Table 2: Comparison of erlotinib/gefitinib in comparable patients These results suggest strongly that erlotinib is more effective than gefitinib in the treatment of East Asian patients. Whilst it is not possible to conduct such an analysis in Caucasian patients (as the manufacturer of gefitinib has not completed a study of gefitinib in this patient population) this evidence is highly suggestive of erlotinib having an efficacy advantage over gefitinib when studied in patients with similar characteristics.	

	PFS HR (Gefitinib or Erlotinib vs Doublet Chemotherapy)	Doublet Chemotherapy Median PFS	Gefitinib Median PFS	Erlotinib Median PFS
OPTIMAL	0.16 {0.11, 0.26}	4.6 months	-	13.7 months
IPASS	0.48 {0.36, 0.64}	6.3 months	9.5 months	-
WJTOG3405	0.49 {0.34, 0.71}	6.3 months	9.2 months	-
NEJSG002	0.30 {0.22, 0.41}	5.4 months	10.8 months	-
First-SIGNAL	0.61 {0.31, 1.22}	6.7 months	8.4 months	-

The Paz-Ares pooling and resultant conclusion of the EMA

The hypothesis of the superiority of erlotinib is also supported by the pooling of phase 2 data undertaken by Paz-Ares et al (see pages 170 and 171 of our submission). The Paz-Ares analysis formed part of the regulatory package submitted to the EMA in support the application to extend erlotinib's use to the first line use of EGFR M+ patients. The EPAR issued by discusses the Paz-Ares

Consultee	Comment	Response
	analysis as follows: *"In the analysis of the data provided in the meta-analysis by Paz-Ares et al, and although there appear to be some gaps in the funnel plots, (which could be a chance finding due to the small number of studies or could be indicative of publication bias) the larger studies lie closer to the vertical reference lines (pooled median PFS) in the plots than the smaller studies and these references are in support of an* ***increasing trend in median PFS with chemotherapy-gefitinib-erlotinib****. Therefore, even in presence of a publication bias, it appears unlikely that it would affect the conclusion of* ***increasing median PFS with erlotinib compared to chemotherapy or gefitinib****. This is also supported by the forest plots."* Erlotinib EPAR p.33 – EMA 2011 In light of this analysis, the resultant conclusion of the EMA and the comparison of erlotinib and gefitinib based upon the IPASS and OPTIMAL studies it appears unreasonably pessimistic to assume that erlotinib and gefitinib are associated with equivalent time in PFS, even though we accept that in the absence of a head-head study the magnitude of any superiority .of erlotinib over gefitinib remains uncertain Whilst we have presented the analyses requested in the ACD in which it was assumed PFS is equivalent for both agents we believe the indirect PFS HR of 0.82 (and resultant median PFS gain of four weeks) applied in the base-case is the still the most reasonable value to use in a base-case analysis. It should be noted that this HR is more conservative than the 0.67 {0.46, 0.96} derived using the indirect comparison suggested by LR*i*G in their ERG report addendum (EURTAC/OPTIMAL vs WJTOG3405/NEJSGS/First-SIGNAL). The ICER estimated using this approach is £16,632.	

Consultee	Comment	Response
Roche	**Conclusions** If more than 91% of patients 'activate' the gefitinib PAS, erlotinib is cost-effective [redacted] compared to gefitinib. This appears highly likely given the evidence currently available (be that from the RCT evidence, audit of real-world patient case notes or expert opinion). NICE approval of erlotinib as an option offers the NHS access to another EGFR TKI in a first line setting [redacted] Approval of erlotinib would grant: • Clinicians the opportunity to utilize an EGFR TKI with demonstrated efficacy in Caucasian patients • Pharmacists the ability to reduce the burden associated with dispensing an EGFR TKI (via use of the simple erlotinib PAS rather than the complex gefitinib PAS) • Clinicians the opportunity to use an EGFR TKI that can be flexibly dosed (something not possible with gefitinib) in response to patient needs • Patients and clinicians *choice* to determine the treatment *they* believe is most appropriate without an increased burden on the NHS If the wider impacts of the PAS are considered in light of the advantages highlighted above and the results detailed in Table 1 the case for NICE approval of erlotinib appears strong.	Comment noted. The Committee discussed the results from the updated analyses where equal efficacy in the progression-free state was assumed for erlotinib and gefitinib and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

Consultee	Comment	Response
Royal College of Pathologists	• Has all of the relevant evidence been taken into account? **Yes** • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? **Yes, in terms of clinical effectiveness. Cost effectiveness is outside the remit of pathology aspects within the ACD** • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? **The provisional recommendation seems to have been made on health economic grounds, so it is not appropriate for the RCPath to comment as pathology was not a factor in the decision making.** • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? **No** • Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document? **No**	Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None received		

Comments received from commentators

Commentator	Comment	Response
Astra Zeneca UK	**Appraisal Consultation Document** 1. Addressing the ACD's statement '...that the patient access scheme for gefitinib is not straightforward and that hospitals may find the patient access scheme for erlotinib easier to administer" (section 4.5) and in section 4.14 where "The Committee considered the administration costs associated with implementing the gefitinib patient access scheme used in	Comment noted. The Committee discussed the administration costs for the gefitinib PAS presented in the manufacturer's model

Commentator	Comment	Response
	the model and concluded that they were reasonable..” we wish to challenge this view and believe that a more robust analysis of the administration costs of the Single Payment Access scheme is required. Our experience with the implementation of the scheme within the NHS has shown that: • Research conducted by AstraZeneca demonstrated that in 25% of NHS centres, Pharmacy Technicians implement the scheme • It does not take 90 minutes to register a new patient on SPA scheme and the sunsequent re-ordering process. Feedback from a recent survey of NHS centres that use the SPA scheme shows that this takes no more than 30 minutes to register a new patient with the majority of respondents stating it takes 6-10 minutes. This significantly reduces the costs per patient managed through the AZ SPA scheme. This feedback is also backed up by survey of NHS centres that currently use the SPA scheme and insight gained from focus groups and advisory boards. We have concerns that Roche seem to have to obtained these costs from Expert Opinion but give no further background to how these values were derived. From the Manufacturer’s Submission (MS), the cost effectiveness model is very sensitive to the administration costs of the Single Payment Access (SPA) scheme and we believe that a more rigorous assessment of the costs is required to ensure that the Committee can truly assess whether erlotinib is value for money based on a transparent and robust evidence base In addition based on ongoing dialogue between AstraZeneca and the NHS, a number of enhancements have been made to improve the NHS’ experience of the scheme. These include: • Multiple deliveries (including extended service to now include Saturday delivery • Multiple patient ordering • Changes to the administration process (reducing burden on the NHS) • Web-based ordering & reporting (providing both convenient ordering & transparent audit of Gefitinib patients)	and in the revised analysis done by the ERG. The Committee concluded that the administration costs of the gefitinib patient access scheme were likely to be nearer the ERG’s estimates rather than the manufacturer’s.
Astra Zeneca UK	1. In the absence of Phase III randomised trials in which gefitinib and erlotinib have been directly compared, AstraZeneca do not feel that it is appropriate to draw conclusions about the relative rate of adverse event reporting for these 2 compounds. Therefore AstraZeneca would like to request that the following statements are withdrawn from the Appraisal Consultation Document	Comment noted. The Committee was aware there was no trial which compares erlotinib and gefitinib. The

<table>
<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
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for erlotinib:

The clinical specialists highlighted that having the choice of two similar treatments enables better management of adverse reactions. The Committee also heard from the clinical specialists that the adverse reactions associated with both these treatments are much less than those associated with chemotherapy but vary (for example, rash is more common with erlotinib and interstitial lung disease with gefitinib). The adverse reactions associated with erlotinib and gefitinib were modest but slightly different.

and

The Committee concluded ..... that from a clinical perspective there may be some advantage to having a choice of tyrosine kinase inhibitors for this patient group to improve the management of the rare but more severe adverse reactions.

In addition to the fact that it may not be appropriate to draw conclusions in the absence of Phase III randomised comparative data, the non comparative data does not support the statement that ILD is more common with gefitinib than with erlotinib, and seems to show that in the first line setting in EGFR mutation positive patients the rates of rash may be similar.

There have been 6 phase III randomised trials of EGFR-TKIs (erlotinib or gefitinib) used as first-line treatment for advanced NSCLC. Four of the 6 studies were conducted in EGFR mutation-positive patients only (NEJ002, WJTOG3405, OPTIMAL and EURTAC) and 2 were conducted in clinically selected patients (IPASS and First-SIGNAL). Patients in IPASS and First-SIGNAL were Asian, never- or light ex-smokers with adenocarcinoma and thus these study populations had higher EGFR mutation rates than unselected patients. It should be noted that none of these were head to head studies of erlotinib vs gefitinib, therefore all comparisons of rates of adverse events are indirect.

The ILD and rash reporting rates in these studies are tabulated below:

<table>
<tr><th>Study</th><th>EGFR-TKI</th><th>Rash (all grades)</th><th>Rash (grades 3 or 4)</th><th>ILD</th></tr>
<tr><td>IPASS (Asian)* (n=1217)</td><td>Gefitinib</td><td>66%</td><td>3.1%</td><td>2.6%</td></tr>
<tr><td>First-SIGNAL (Korean)* (n=313)</td><td>Gefitinib</td><td>72%</td><td>29.3%</td><td>1.3%</td></tr>
</table>
</td><td>Committee considered the adverse reactions reported in the erlotinib trials submitted by the manufacturer and heard the opinion of clinical specialists. The Committee concluded that further first-line treatment options for patients with locally advanced or metastatic EGFR mutation-positive NSCLC would be valuable for clinical practice.</td></tr>
</table>

Commentator	Comment					Response
	NEJ002 (Japanese) (n=228)	Gefitinib	81%	5.3%	5.3%	
	WJTOG3405 (Japanese) (n=172)	Gefitinib	74%	2.3%	2.3%	
	OPTIMAL (Chinese) (n=165)	Erlotinib	75%	2%	0%	
	EURTAC (European) (n=174)	Erlotinib	80%	13%	1%	

**please note that these studies were conducted in a clinically selected population, not EGFR mutation-positive only populations*

Based on the data presented above, the rates of rash in EGFR mutation-positive patients appear similar for 1st-line gefitinib and erlotinib.

On considering the figures for ILD it might appear that the reporting rates for gefitinib are slightly higher than those for erlotinib, however the patient numbers in most of these studies are small and therefore it is difficult to determine whether these percentage values are truly different.

In addition, a large proportion of the gefitinib data has been generated in a Japanese population. It is acknowledged that ILD reporting rates for all treatments are higher in this population, and this is demonstrated specifically for gefitinib by the AstraZeneca cumulative reporting rates for ILD in patients receiving IRESSA. The reporting rates of ILD are expressed in number of patients who experienced ILD per 100 patient-years of IRESSA patient exposure.

	Cumulative reporting rates for ILD-type events as of 05 January 2012[a]		
	No. of patients reporting ILD	**Total patient exposure (patient-years)**	**No. of patients per 100 patient-years**
Japan	2286	62012	3.69

Commentator	Comment	Response
	EU 142 7555 1.88 Rest of World (RoW) excluding Japan[b] 597 82626 0.72 South-East (SE) Asia[c] 154 46514 0.33 **Total (Global) 2883 144638 1.99** [a] These estimates of reporting rates include all reports of ILD-type events in IRESSA-treated and treatment-blinded patients, regardless of reported causality [b] Including SE Asia, US and EU data. [c] SE Asia comprises data from China, Hong Kong, Korea, Philippines, Malaysia, Indonesia, Singapore, Thailand and Taiwan Recently data has become available for erlotinib in the Japanese patient population from the Japanese Post Marketing Surveillance (PMS) Study (Scrip 10 February 2012). Detailed safety data is available for 3488 patients treated with erlotinib. These patients were mainly pre-treated. The reporting rate for ILD events was 5%, higher than the rate seen non-Japanese patients in the OPTIMAL and EURTAC studies, but similar to the gefitinib Japanese PMS study (also mainly pre-treated patients) where the incidence of ILD was 5.8%. We believe that the Committee should request similar data from Roche to enable an informed and balanced conclusion is reached on ILD and EGFR-TKIs.	
Astra Zeneca UK	2. We would like to challenge the Appraisal Committee's conclusion that erlotinib offers an advantage regarding the dose variation available. We believe that the dose variation is only an advantage when the erlotinib's rash is taken into account. The Appraisal Committee does not take into account the increased cost of nursing time, drug wastage and outpatient visits when adjusting the erlotinib dose due to rash.	Comment noted. The Committee noted the availability of different strength tablets and heard from the clinical specialists that the dose may be varied in some patients.
Astra Zeneca UK	**Evaluation Report** 1. We believe that the ERG's recommendation of pooling EURTAC and OPTIMAL is inappropriate. We believe their recommendation was based on an incorrect assumption that Roche assessed	Comment noted. The Committee considered the indirect comparison

Commentator	Comment	Response
	the similarity of the studies using median PFS (see section 3.23 of the Appraisal consultation document) when in fact it was the hazard ratios they compared in their assessment of heterogeneity (see figures 22 and 23 of the manufacturer submission where the forest plots with the fixed- and random-effects HRs are displayed). Given the negligible overlap of the confidence intervals for the treatment effect (measured using the hazard ratio) in the two studies, it is not appropriate to pool these heterogeneous effects together to estimate the overall efficacy of erlotinib; quoting an average value for the intervention effect when the magnitude of the treatment effect observed in each study is not consistent and is likely to be misleading and unreliable.	presented by the manufacturer. The Committee was not convinced that an indirect comparison could be used with the existing data to obtain a reliable estimate of the efficacy of erlotinib compared with gefitinib, given the heterogeneity of the populations included and the variations in prognostic factors within the populations.
CSAS	On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. We are in agreement with the recommendations in the ACD not to recommend erlotinib for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice. • **Doublet chemotherapy was not considered as an alternative first-line treatment.** Clinical trials have compared erlotinib with platinum doublet chemotherapy. The manufacturer submitted no evidence for the cost effectiveness of erlotinib compared to doublet chemotherapy. The Appraisal Committee, based on the input of clinical specialists, has agreed that platinum doublet chemotherapy is rarely used as first-line treatment for patients with EGFR-TK mutation positive NSCLC, and considered gefitinib only to be the appropriate comparator. • **No studies directly compare erlotinib with gefitinib.** Gefitinib is current standard first-line treatment for this patient group and no direct comparison between these treatments is available. Based on the input of clinical specialists that these are similar treatments with similar efficacy, the Appraisal Committee concluded that erlotinib and gefitinib should be assumed to have equal efficacy in terms of median progression free survival, about 9.7 months for erlotinib compared to 5.2 months for platinum doublet chemotherapy. • **There is insufficient evidence to assess the cost-effectiveness of erlotinib compared to gefitinib.** The Appraisal Committee did not have sufficient information to assess the most plausible ICER for erlotinib compared to gefitinib. They disagree with key assumptions made	Comment noted. The Committee discussed the results from the updated analyses where equal efficacy in the progression-free state was assumed for erlotinib and gefitinib and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

Commentator	Comment	Response
	in the manufacturer's model, and have requested an additional analysis that assumes equal progression free survival and utility of the progression free state for the main comparison (erlotinib versus gefitinib). • **Adverse events associated with erlotinib treatment were moderate.** The severity of adverse events was similar between erlotinib and gefitinib, however, each had a different profile of adverse events. Clinical specialists have indicated that there may be an advantage to having a choice between treatments to improve the management of patients experiencing more serious side effects. • **The manufacturer may have underestimated the eligible population.** The manufacturer's estimate of 0.76 per 100,000 population eligible for treatment with first-line erlotinib reflects internal assumptions regarding the proportion of NSCLC patients who will undergo EGFR testing prior to initiating a first-line treatment regimen. The manufacturer estimates that only 50% of patients will receive such testing or have a specimen sufficient for testing. The committee, however, reports that EGFR testing is now standard practice in this patient group. • **The cost of erlotinib treatment is subject to a confidential patient access scheme.** This is based on the manufacturer's eligibility algorithm. The cost of treating a single patient for 10 months is expected to be in excess of £10,000. • **The cost of erlotinib depends on the dose.** There are three available doses of erlotinib. The dose is reduced as appropriate by clinicians. Cost estimates reflect the recommended maximum dose of 150mg. It is not clear how many patients would be eligible for a reduced dose. • **Erlotinib is covered by a simple discount on the Patient Access Scheme (PAS).** Gefitinib is also covered by a scheme; all patients who receive at least 3 months of treatment incur a flat charge of £12,200. The erlotinib PAS agreement is likely to be more straightforward to administer.	
Lilly UK	Lilly UK has no comments on the appraisal consultation document.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS commissioning manager	1(Appraisal Committee's preliminary recommendations)	We agree with and support the NICE Appraisal Committee's views that there is not enough info, in particular with regards to a sensitivity analysis of likely costs comparing current first-line treatment with Gefitinib. Rough calculations: We have on average 1,236 new cases of lung cancer each year. 85% (~1,051 patients) of these will be non-small cell lung cancer who would qualify for treatment with either Gefitinib or Erlotinib. Assuming Gefitinib is a flat rate cost of £12,200 and Erlotinib is £16,315 for 10 months treatment (this is the median survival cited from the research papers), Erlotinib is £4,115 more expensive per patient treated. So worse case scenario is we are looking at £4.3 million extra per year. If we were to get a 14% discount via a Patient Access Scheme as suggested, we are still looking at a worse case scenario of £1.8 million extra per year. Some caveats not included here due to word limit. The usual financial concerns apply ? approval of drugs mid way through a financial year where we have not set aside funds for means having to find these funds by cutting back on other commissioned services. £4m could be disastrous.	Comment noted. The Committee discussed the results from the updated analyses where equal efficacy in the progression-free state was assumed for erlotinib and gefitinib and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.
NHS Professional	Note:	I work for an NHS commissioning organisation PCT that has considered this technology in this indication and found the case for use to be favourable	Comment noted. The Committee discussed the results from the updated analyses where equal efficacy in the progression-free state was assumed for erlotinib and gefitinib and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

* 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
	1(Appraisal Committee's preliminary recommendations)	Clinical studies demonstarte improved progression free survival compared to platinum based therapy Erlotinib is considered to offer some advantages over gefitinib, the current standard treatment for patients with this form of lung cancer. Efficacy data is available for both European and Asian populations, and managing adverse effects with dosing adjustment is more easily achieved with erlotinib due to therange of strengths available. The Group consider that evidence is sufficient to support commissioning erlotinib as an option for this indication where the clinician considers the benefits justify its use and the patient understands that it will be used instead of the NICE approved treatment, gefitinib. NICE are due to issue definitive guidance on the use of erlotinib in this indication in June 2012. Until this time, the manufacturer has undertaken to provide erlotinib to the NHS at a discount, if the treating provider agrees to (*This sentance was unfinished in the comment)*	Comment noted. The Committee discussed the results from the updated analyses where equal efficacy in the progression-free state was assumed for erlotinib and gefitinib and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.
	4 (Consideration of the evidence)	The PCTs in the SW peninsula considered the clinical evidence and the financial uncertainties of erlotinib and gefitinib. The clinical trial data for erlotinib demonstrates improvements in progression free survival over standard platinum based chemotherapy. Whilst there are no data comparing erlotinib to gefitinib the prolongation in progression free survival noted for erlotinib is considered of particular clinical relevance as the study population more closely mirror the UK population than the studies supporting gefitinib. The cost effectiveness case largely depends upon the patient access schemes available. The geftinib scheme in particular is highly uncertain because of the high initial costs £12,200 + VAT that must be paid. Assumptions about expected treatment duration are key and this is subject to uncertainty. The erlotinib scheme is more straightforward and applicable for the duration of treatment, whatever that proves to be (either due to progression or adverse events).	Comment noted. The Committee discussed the results from the updated analyses where equal efficacy in the progression-free state was assumed for erlotinib and gefitinib and the Committee concluded that at the price agreed under the new patient access scheme erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.