**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**MULTIPLE TECHNOLOGY APPRAISAL**

# Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175) [ID620]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Documents (ACD1/2/3)**

2. **Consultee and commentator comments on the Appraisal Consultation Document 3 (released July 2014)** from:
   - Roche
   - Royal College of Physicians
   - Roy Castle Lung Cancer Foundation

*AstraZeneca, Department of Health and Royal College of Nursing responded to say they had no comments*

3. **Comments received on the relevance of the PPRS position statement in relation to this appraisal** from:
   - Roche Products

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Health Technology Appraisal

## Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (review of NICE technology appraisal guidance 162 and 175)

## Response to consultee, commentator and public comments on the Appraisal Consultation Documents (ACD1/2/3)

**Definitions:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

**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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comments received from consultees

| Consultee | Comment | Response |
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| AstraZeneca | AstraZeneca has no further comments on the ACD for erlotinib and gefitinib. | Comment noted. No action required. |
| Roche Products (1) | Thank you for providing the opportunity to comment on the ACD for the above appraisal. We are disappointed that this draft guidance will significantly set-back the treatment of people with Lung Cancer.<br><br>The majority of people with this disease are unable to tolerate cytotoxic chemotherapy – erlotinib is their only effective treatment option and can provide two months of additional life[1]. The ERG ICER in this population is £54,686/QALY gained.<br><br>We note that this appraisal is expected to continue beyond the time at which NICE's proposals for 'Value Based Assessment' (VBA) will have been implemented.<br><br>The QALY multiplier required for approval under the ERG base-case in this group is not substantially above the range quoted in the VBA consultation document (2.7 compared to 2.5). Given the high 'burden of illness' and high 'wider societal impact' associated with Lung Cancer, we would welcome consideration of erlotinib under this new approach. We are committed to finding a long term solution to ensure people with Lung Cancer continue to benefit from erlotinib and would welcome further dialogue on this issue.<br><br>*1. LRiG ID620 Assessment Report* | Comments noted.<br><br>NICE technology appraisal guidance 162 did not recommended erlotinib for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.<br><br>The Committee noted that in the Value Based Assessment consultation document, it was proposed that burden of illness and wider societal impact would be added to the existing set of modifiers that an Appraisal Committee is able to take into account, and that 2.5 represents the maximum weighting that the Appraisal Committee should consider when taking into account the cumulative impact of all the modifiers. Furthermore, the Committee was aware that following consultation on value based assessment of technologies, no changes to NICE's Guide to the |

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| | | methods of technology appraisal are being made in the short term and that the current end-of-life treatments protocol is being retained in its current form, while NICE carries out further work. Based on NICE's current methods for appraising technologies and the ICERs presented, the Committee concluded that erlotinib could not be recommended for this population. For further details, please see section 4.3.21 of the final appraisal determination. |
| Roche Products (2) | Thank you for giving us the opportunity to comment on the ACD. We believe this appraisal raises an important issue – an issue which must be addressed if the final recommendation is to be considered a sound and suitable basis for the issuance of guidance to the NHS.<br><br>Under the terms of the Pharmaceutical Price Regulation Scheme 2014, the total spend on branded medicines in the UK is capped. The scheme caps the budget with annual growth limited to 0% in 2014 through to 1.9% in 2018.<br><br>Forecast growth is significantly higher at 3.87% in 2014 – when the expected growth rates are compounded, by 2018 the uncapped spend on branded medicines will be 17.59% above the current level whilst the agreed spend level with the cap will be only 5.6% above the current level.<br><br>This will result in an anticipated overspend above the cap in the region of £386m in 2014 rising to £1202m in 2018*. All expenditure which exceeds the cap will be rebated by industry.<br><br>This PPRS agreement raises an interesting question. If expenditure on branded medicines remains above the agreed cap level in the scenario of a positive or | Comments noted. The Committee discussed the relevance of the 2014 PPRS, and specifically the payment mechanism. It accepted the conclusion in NICE's position statement 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of erlotinib and gefitinib. It therefore concluded that the PPRS payment mechanism was not applicable for the consideration of cost effectiveness of erlotinib and gefitinib. Please see sections 4.3.27 to 4.3.29 of the final appraisal determination. |

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| | negative NICE decision (as it will in the case of erlotinib) is it reasonable for an Appraisal Committee to make a decision under the assumption that funding the medicine in question will come at an additional cost to society?<br><br>In the case of this appraisal, decommissioning erlotinib in patients unsuitable for docetaxel will result in a reduction in spending by the NHS; however this will result in an equivalent reduction in the PPRS rebate paid by industry. There is an opportunity cost associated with this loss in rebate which must be considered by the Committee.<br><br>We appreciate this is a complex issue that has not been discussed in an Appraisal to date and one that may need to be considered further by the Institute. However, we feel this is something which must be addressed if the Committee's decision is to be considered a sound and suitable basis for guidance to the NHS. | |
| National Lung Cancer Forum for Nurses | Please accept this additional summary on behalf of NLCFN.<br><br>We agree that testing for EGFR-TK mutation status does occur for most people with a diagnosis of non small cell lung cancer of adenocarcinoma subtype. However, many people with a non small cell lung cancer other than an adenocarcinoma (such as NOS or mixed cell type) do not routinely have access to EGFR-TK testing.<br>People with a non small cell lung cancer EGFR –TK mutation unknown, who are without access to EGFR-TK testing, do not appear to have been considered within the scope of this recommendation. It is important that these people are not disadvantaged.<br><br>We acknowledge that extending survival and improving quality of life are important to people with non small cell lung cancer. Patient's frequently highlight to us when life expectancy is short spending less time in hospital, at hospital appointments, and complications of treatments are key considerations when considering second-line treatment. As the consultation identifies only a small proportion of people are | Comments noted. The clinical specialists stated that most patients now have a mutation test before starting first-line treatment and emphasised the importance of testing all patients.<br><br>The patient expert emphasised that extending survival and improving quality of life are important to people with non-small-cell lung cancer, as is spending less time at the hospital because they have a short life expectancy. The Committee recognised the importance of having clinically effective and tolerable treatment options for people with non-small-cell lung cancer that has progressed after prior chemotherapy.<br><br>The Committee heard from the clinical specialists that in clinical practice docetaxel is preferred |

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| | suitable for second-line treatment.<br><br>We would like to highlight that the patient experience is often more unpleasant with docetaxel and tolerated far less well than erlotinib. | despite its toxicity because, in their opinion, docetaxel is clinically effective compared with erlotinib. The Committee was also aware that direct evidence comparing erlotinib with docetaxel showed erlotinib to be less clinically effective.<br><br>The Committee noted that although erlotinib was considered to be better tolerated than docetaxel, the health-related quality of life and the cost associated with managing adverse reactions had been accounted for in the cost-effectiveness estimates.<br><br>Please see section 4.3.20 of the final appraisal determination. |
| Roy Castle Lung Cancer Foundation | • We are very disappointed that the Appraisal Committee's third preliminary decision is not to recommend Erlotinib for EGFR mutation negative patients, as a second line therapy. This will limit a therapy option which for some years has been standard clinical practice. This would adversely affect future treatment options for many patients affected by this devastating disease.<br><br>• We welcome the recommendations that Erlotinib and Gefitinib are available for use after chemotherapy, in EGFR mutation positive patients, in whom there was a delayed confirmation of EGFR mutation status. The number of patients impacted by these recommendations, however, is extremely small.<br><br>• We also welcome the recommendation that Erlotinib is available for use after chemotherapy, in EGFR mutation status unknown, as outlined in Paragraph 1.2. Again, however, the number of patients impacted by this will | Comments noted. |

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| | be very small.<br><br>Our comments below are confined to those patients, in whom EGFR mutation status is negative (including those where it is unknown but assumed to be negative). Many of these points were raised in our response to the first ACD, back in February 2014. We do not believe that they have been adequately addressed. The questions we are asked to comment on are as follows:<br><br>**i) Has all of the relevant evidence been taken into account?**<br>We do not have any additional evidence. However, we believe the Committee has failed to take sufficient account of the differences between Docetaxel (the only other anti-cancer drug therapy available in this indication) and Erlotinib, as described in section (ii) below. We also do not think that the Committee has addressed the implications of a false negative EGFR mutation test result.<br><br>**ii) Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?**<br>Comments: No. There are two particular issues.<br><br>Comment 1: We remain deeply concerned that the Appraisal Committee has placed so much emphasis on the TAILOR study, in its assessment, deliberations and decision. Whilst we understand that this represents the only published direct comparison of Docetaxel and Erlotinib, we are very aware that this Italian Study does not reflect practice here in the UK. In the TAILOR Study, Docetaxel is given weekly, whereas in the UK it is administered three weekly. Also, on discussion with clinicians, we note the side effects of Docetaxel reported in this Study are considerably less than we see in practice here (in particular, the febrile neutropenia rate). We are aware that international consensus has concluded that the result of the TAILOR Study should not be used to make decisions about second line therapy in non-small cell lung cancer. It is deeply worrying that should this Appraisal Committee decision be finalised, it will ensure a change to standard clinical practice | Comments noted. The Committee heard from the clinical experts that erlotinib is now essentially regarded as a targeted therapy for mutation-positive patients only (see section 4.3.9 of the final appraisal determination). The Committee noted that although erlotinib was considered to be better tolerated than docetaxel, the health-related quality of life and the cost associated with managing adverse reactions had been accounted for in the cost-effectiveness estimates (see section 4.3.20 of the final appraisal determination). The Committee noted that the Assessment Group's scenario analysis was not plausible but acknowledged that some people may have a preference for erlotinib because it is orally administered. However, it concluded that including a plausible estimation of the health-related quality-of-life benefits of oral treatment would not change its conclusion about the cost effectiveness of erlotinib in the EGFR-TK mutation-negative population for whom docetaxel is suitable (see section 4.3.23 of the final appraisal determination).<br><br>Comments noted. The Committee discussed the generalisability of the TAILOR trial to clinical practice in England. The Committee also heard |

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| | for a significant number of patients, based on a study of questionable relevance to our UK practice.<br><br>Comment 2: We believe that the Committee has failed to recognise that Erlotinib is not simply an alternative chemotherapy to Docetaxel, but is a totally different type of therapy, with a very different side effect profile and administration route, making Erlotinib much more acceptable for patients. Whilst we understand NICE's focus on cost effectiveness, surely patient choice and acceptability are also of relevance?<br><br>• The side effects of Erlotinib are much less significant than Docetaxel – for which severe neutropenia can be life threatening.<br>• Many patients comment on the 'toxic' nature of Docetaxel.<br>• As an oral medication, Erlotinib does not involve repeated day case admissions for iv administration – offering a much greater prospect of treatment closer to home. We are ever mindful that, in the main, this group of patients has a short life expectancy. It is important to ensure that they are able to spend as much time as possible away from the hospital setting.<br><br>In this group of patients, at a second line treatment stage, there would be a number, who would reject Docetaxel as a treatment option, based on the side effect profile. Should Erlotinib be denied to this patient group, then no recommended anti-cancer therapy will be available.<br><br>Also, for those of borderline fitness for Docetaxel, at present, clinicians can offer oral Erlotinib as a more easily tolerated anti-cancer therapy to this patient group. Should this option be denied, then only the more toxic option will be available.<br><br>**iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br>Comments: No, there are three issues. | from the clinical experts that increasing the frequency of docetaxel infusion had become more common in clinical practice in the preceding 12 months because of the results from the TAILOR trial. The Committee considered that the results of the TAILOR trial were relevant to people in England with non-small-cell lung cancer whose disease had progressed after chemotherapy and whose tumours tested negative for EGFR-TK mutations. The Committee concluded that based on the available evidence and clinical practice in England, erlotinib is less clinically effective than docetaxel in the EGFR-TK mutation-negative population. For further details, please see section 4.3.10 and 4.3.14 of the final appraisal determination.<br><br>Comments noted. Please see above for response to comment 2. The Institute takes into account the clinical and cost effectiveness of a technology, along with other considerations (see section 6.2 of NICE's Guide to the methods of technology appraisal), when issuing guidance to the NHS. The Institute does not set the budget for the NHS. The appropriate objective of the Institute's technology appraisal programme is to offer guidance that represents an efficient use of available NHS and personal social services resources. When estimating clinical and cost effectiveness, the reference case specifies the methods considered by NICE (consistent for every technology and for all conditions) to be the most appropriate for the Appraisal Committee's purpose and consistent with |

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| | Comment 1: The previous Technology Appraisal confined the use of Erlotinib in this indication, to patients who were suitable for Docetaxel therapy. As in (ii) above, this Appraisal Committee decision, if finalised, will remove the option of active second line anti-cancer therapy for these patients. As noted in (ii) above, we are deeply concerned that this decision is being made based on a single study of questionable relevance to UK clinical practice. We therefore do not conclude that assumptions and assessments made in coming to this provisional recommendation are sound.<br><br>Comment 2: We note that in EGFR negative patients, unfit for Docetaxel, where the comparator is 'best supportive care', as with the original appraisal, it is concluded that Erlotinib is not deemed cost effective. We take this opportunity to remind the Appraisal Committee that, for this patient group, Erlotinib remains the only active anti-cancer therapy option and with this decision, access will continue to be denied.<br><br>Comment 3: Across the globe, Erlotinib has become a standard therapy option, in second line, for patients with non-small cell lung cancer. Clearly, we do not wish to see the NHS in England deprive lung cancer patients of therapies routinely available elsewhere. Changing the current standard of care for English patients will not only have a negative impact on patients but, will limit English participation in clinical research in this patient group, amongst whom, there is still much unmet need.<br><br>**The patient's viewpoint:**<br>Finally, as a lung cancer charity, we have contact with patients through our social media outlets and on line forums. As indicated in our response to ACD1, the public announcement of that particular Appraisal Committee Document provoked some of the most comments on any single topic, we have seen. They serve as a reminder of the impact of a negative decision on real patients and their families.<br><br>• "My mum has been taking Tarceva as a second line treatment since June and she is stable and enjoying life again..... . Apparently, you can, it seems | an NHS objective of maximising health gain from limited resources. |

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| | put a price on life... . Mum nearly lost all her will to live. ... Tarceva is saving her life."'<br><br>• "..... I have been on Tarceva since August 22 2013 and although I am not EGFR positive, it seems to be working, at least keeping it at bay. ....."<br><br>• "I cannot believe that a decision like this can be made. Yet, if you live in Scotland, it won't affect you. If this is carried out, it will seem like a death sentence when chemo isn't an option. ....."<br><br>The sheer disappointment expressed after ACD 1 was replaced by many positive comments, on the announcement of ACD 2, with a positive recommendation in EGFR mutation status negative patients. Sadly, this ACD 3, has reverted to the negativity of ACD 1. This has been a frustrating appraisal process for those lung cancer patients, who have been following its progress.<br><br>We welcome the ongoing nature of the appraisal process and hope that the Appraisal Committee will re-consider their decision at the earliest opportunity and also include, within its recommendations, that Erlotinib is also available within the NHS, in the second line setting, as a therapy option for EGFR mutation negative patients. | |
| Royal College of Nursing | This is to inform you that nurses within this area of health have reviewed the ACD on behalf of the Royal College of Nursing and have informed us that there are no comments to submit at this present time. Thank you for the opportunity to participate. | Comments noted. No action required. |
| Royal College of Pathologists | I am just writing to inform you that the Royal College of Pathologists does not have any comments to make on this ACD. | Comments noted. No action required. |

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| Royal College of Physicians | I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who work together to produce joint responses to NICE oncology consultations. We are grateful for the opportunity to consider the above ACD3 and would like to make the following comments.<br><br>Our experts note that section 1.3 states:<br><br>*'Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-negative.'*<br><br>This represents a disappointing reversal of the previous decision, which could remove an established treatment option for patients with non-small cell lung cancer (NSCLC). The decision would be at odds with treatment guidelines from Europe and North America and would limit clinician and patient choice in a disease group where survival in UK patients is amongst the poorest in the western world.<br><br>With regard to whether all the evidence has been taken into account and whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence:<br><br>Although a range of clinical trial data has been used to support the economic modelling with regard to the costs associated with docetaxel versus erlotinib treatment, it is unarguable that patients enrolled in clinical trials are younger, fitter and have less co-morbidity than typical NSCLC patients, which results in fewer complications of treatment. Furthermore, G-CSF prophylaxis, which was used in all the clinical trials included in the appraisal review, is not recommended by NICE (CG151) and is therefore not available for use. During the consultation observations of clinical specialists, comments from professional organisations and audit data have consistently stated that real life febrile neutropenia and hospital admission | Comments noted.<br><br>NICE understands your disappointment but unfortunately an error was identified in the economic model used to inform the Appraisal Committee's decision making during the consultation of the second appraisal consultation document. Consequently, this had a material effect on the Committee's recommendations for the EGFR-TK mutation-negative population.<br><br>It is important to recognise that treatment guidelines are generally informed by clinical-effectiveness evidence. The Institute takes into account the clinical and cost effectiveness of a technology, along with other considerations (see section 6.2 of NICE's Guide to the methods of technology appraisal), when issuing guidance to the NHS. The Committee also heard from the clinical experts that erlotinib is now essentially regarded as a targeted therapy for mutation-positive patients only (see section 4.3.9 of the final appraisal determination).<br><br>Comments noted. Please note that the Assessment Group's model assumed that febrile neutropenia was treated in the hospital. The Committee considered comments received during consultation and the additional data on the incidence of febrile neutropenia presented by the Assessment Group in its second addendum. The Committee |

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| | rates observed with docetaxel treatment are significantly higher than those used for economic modelling by the ERG (a view supported by published literature). Also, that this undoubtedly carries a substantial financial burden to the NHS, in addition to the detrimental effect on quality of life for patients and increased resource-use for overstretched NHS inpatient services.<br><br>It is hoped by clinicians and patients alike that erlotinib will not be removed unnecessarily as an option for the second line treatment of advanced EGFR wild type (mutation negative) NSCLC, particularly as docetaxel may not be suitable alternative treatment for all patients and the 'real costs' associated with docetaxel have been underestimated. | acknowledged that there was considerable variability, and therefore uncertainty, around the most plausible incidence rate for febrile neutropenia. The Committee concluded that, for all incidence rates of febrile neutropenia suggested during the course of the appraisal (up to 41%), erlotinib did not represent a cost-effective use of NHS resources for the EGFR-TK mutation-negative population (see section 4.3.14 of the final appraisal determination). |
| Royal College of Nursing | Feedback suggests that there are no comments to make on this document and therefore the Royal College of Nursing will not be making any comments on this occasion.<br>Thank you for the opportunity to contribute to this appraisal. | Comments noted. No action required. |
| Department of Health | Thank you for the opportunity to comment on the appraisal consultation document for the above multiple technology appraisal.<br>I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation. | Comments noted. No action required. |

## Comments received from commentators

| Commentator | Comment | Response |
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| British Thoracic Oncology Group | The BTOG steering comittee agree with the preliminary recommendations 1.1 and 1.2 of 'appraisal consultation document 1'. | Comments noted. |

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| | The BTOG steering committee disagree with recommendations 1.3 and 1.4 of 'appraisal consultation document 1'.<br><br>**• Has all of the relevant evidence been taken into account?**<br><br>No; the committee have not adequately considered the possibility of a false negative EGFR mutation test result. This would arise due to genotyping of a tumour specimen with inadequate tumour tissue, resulting in failure of the EGFR genotyping technology applied to detect the EGFR mutation.<br><br>No: for recommendation 1.4, the committee have not determined what is classified as an unobtainable EGFR mutation test due to inadequate sample or poor DNA quality. This is a subjective measure of sample or DNA quality, and would be contingent on subjective evaluation, and is therefore prone to considerable bias Nationally.<br><br>**• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br><br>No; the DSU meta-analysis of febrile neutropenia rates for docetaxel grossly under-estimates true incidence. Moreover, in the trials pooled, prophylaxis with GCSF was available. Due to implantation of NICE CG151, GCSF prophylaxis is not longer recommended, and febrile neutropenia rates (and associated management costs) will be considerably higher, and has been reported in England at 41% (Sharma Lung Cancer (2009) vol 63, suppl1;S6).<br><br>No: The committee has put considerable weight on the Tailor data in reaching its recommendation. Further, flaws in the study and the caveats in interpretation of the data were not included in the consultation document. The Tailor study was | The recommendation in the final appraisal determination note that "Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, only if the company provides erlotinib with the discount agreed in the patient access scheme."<br>The views of clinical experts were considered by the Appraisal Committee when formulating its recommendations.<br><br>Please note that the Assessment Group's model assumed that febrile neutropenia was treated in the hospital. The Committee considered comments received during consultation and the additional data on the incidence of febrile neutropenia presented by the Assessment Group in its second addendum. The Committee acknowledged that there was considerable variability, and therefore uncertainty, around the most plausible incidence rate for febrile neutropenia. The Committee concluded that, for all incidence rates of febrile neutropenia suggested during the course of the appraisal (up to 41%), erlotinib did not represent a cost-effective use of NHS resources for the EGFR-TK mutation-negative population (see section 4.3.14 of the final appraisal |

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| | conducted over many years, with changes to the primary outcome and without appropriate protocol-driven assessments of end points, particularly the lack of regular tumour response rate assessment for PFS data. The response rate in the Tailor study was grossly different to data from other studies. It was the conclusion of ASCO that "the results of the Tailor study should not be used to make decisions about second line therapy in NSCLC".<br><br>**• Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br><br>No: trial data documented in the ERG report (IPASS trial, Mok et al NEJM) clearly demonstrated that despite clinical selection, only 60% of patients harboured EGFR mutation. As a consequence, routine EGFR genotyping regardless of clinical features has been routinely implemented in the UK (and globally) following from NICE guidance TA192 and TA258. To suggest that clinical selection should be employed for genotyping is contrary to study data.<br><br>No: to suggest that for patients with unknown genotype, that response is an indicator to continue therapy goes directly against the clinical data, which clearly demonstrate a radiological response rate of 56% (LUX 3 trial) - 80% (OPTIMAL trial). Therefore at least 20% of patients with unknown genotype and EGFR mutation positive would have erlotinib withdrawn inappropriately. For these patients, withdrawal inappropriate would lead to tumour flare (Riely et al Clinical Cancer Research 2007; Chaft et al. Clinical Cancer Research 2011), and poor outcomes, especially if further systemic therapy was not possible.<br><br>No: the recommendation 1.4 to allow erlotinib to patients with tissue unsuitable for genotyping will perversely drive clinical decision making to artefactually increase the number of tumour samples from patients deemed (subjectively) unsuitable for EGFR | determination).<br><br>The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the companies' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment Report.<br><br>The clinical specialists stated that most patients now have a mutation test before starting first-line treatment and emphasised the importance of testing all patients. |

| Commentator | Comment | Response |
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| | genotyping.<br><br>**• 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**<br><br>Yes: with respect to recommendation 1.4. Considerable evidence supports the fact that EGFR mutation is commoner in never-smokers, females, and East Asian ancestry. However, considerable evidence demonstrates that this relationship is not robust and multiple patient series have demonstrated EGFR mutations occur in patients with current or ex-smoking backgrounds, and not of East Asian ancestry (30% in one series; Leary Eur J Canc 2012;48:61-7). Therefore, to recommend possible erlotinib use in a sub-group selected by gender, race, or smoking status is wholly discriminatory. | The Committee noted a comment received in response to the 'appraisal consultation document 1' that recommending erlotinib for use in a subgroup of patients whose tumours are likely to test positive for EGFR-TK mutations based on sex, race, or smoking status is discriminatory. The Committee agreed that its recommendations do not constitute detrimental treatment of patients whose disease is likely to test negative for EGFR-TK mutations and therefore its recommendations were fair and did not constitute an equality issue. Please see section 4.3.26 of the final appraisal determination. |
| Healthcare Improvement Scotland | In considering this document it is important from the Scottish perspective to point out that there are already differences between England and Scotland in approval for use of these drugs. Also we should note that in both countries the 'goalposts' have changed since initial policies on use of these drugs, as now all patients will have had some attempt to get EGFR mutation status at diagnosis.<br><br>The evidence provided here is a comprehensive listing of all trials and the cost effectiveness calculations have been done thoroughly with due consideration for all potential influencing factors.<br><br>It is standard practice now for both England and Scotland that patients with positive EGFR mutation status should receive EGFR TK inhibitors first line, with which this document concords. The document also acknowledges that if treatment has been | Comments noted. No action required. |

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| | commenced in advance of EGFR status being known and the patient then turns out to be positive, they should be switched to oral TKI. This makes clinical sense and is not strictly speaking 'second line' therapy.<br><br>With regard to patients who are EGFR unknown or negative the document does not issue guidance on use of gefitinib as this drug has not been licensed for any other than mutation positive patients. This is entirely appropriate, (and in Scotland even in first line EGFR positive patients this drug is not authorised for use but rather erlotinib is indicated)<br><br>There is a lot of debate in the document about the relative efficacy/cost effectiveness/merits of erlotinib versus docetaxel as an alternative second line therapy. Although both are licensed and approved for use at present in Scotland, as second line treatment options, the results suggest that in EGFR negative or unknown patients the benefits of erlotinib are at best marginal. There is a comment that clinical practice is out of step with NICE guidance in that erlotinib is commonly prescribed for patients of PS 2 as second line therapy when such patients would not be fit for docetaxel. This is also the case commonly in Scotland in terms of prescribing practice so the current use of erlotinib is higher than should be on basis of actual license/approval.<br><br>The document concludes that there is not sufficient evidence to recommend erlotinib as second line therapy in patients where EGFR status is negative or unknown. If this recommendation is endorsed (and it does appear appropriate on the basis of evidence) then this will put NICE out of line with Scotland where erlotinib continues to be approved in this indication.<br><br>Finally as a general comment it was helpful to have the criteria for 'end of life' access to medicines spelled out concisely : namely survival less than 24 months, expected benefit of intervention anticipate as at least 3 months and total no patients | |

| Commentator | Comment | Response |
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| | in England of less than 7000. These are useful markers – was not sure if SMC have applied similar criteria to their recently revised processes. | |

## Comments received from members of the public

| Role* | Section | Comment | Response |
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| General public (1) | 1 | No one conforms to set statistics! There are people without mutations doing well on these drugs. Why does the UK have to go backwards in medicine when all other countries advance! | Comments noted. Recommendations are based on evidence of both clinical and cost effectiveness. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective (Social Value Judgements - Principles for the development of NICE guidance; principle 5). |
| General public (1) | 2 | Wouldn't you want to prolong your loved ones life if you knew that this drug could help! Cancer don't care who it strikes so don't think that just because you may not smoke you won't one day be hit with a lung cancer diagnosis! You may need this drug then! | Comments noted. The Committee is required to resist pressure to make decisions that are not in the broad public interest (Social value judgements [SVJ] Principle 12). |
| General public (1) | 3 | Cancer affects 1 in 3 people. By taking away the chance of having accessibility to drugs that have proven positive effects is ridiculous. Whatever the percentage the fact is there is a percentage which means there's a chance! And every second we have in life cannot be measured in value!!! | Comments noted. Recommendations are based on evidence of both clinical and cost effectiveness. The views of clinical experts and patient/carer representatives were also considered by the Appraisal Committee when formulating its recommendations. For both legal and bioethical reasons those undertaking technology appraisals |

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', '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 |
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| | | | and developing clinical guidelines must take account of economic considerations (Social Value Judgements - Principles for the development of NICE guidance; principle 5). |
| General public (1) | 7 | Life is priceless- don't stop a drug that helps because of cost! You could be taking my Daddy away from me sooner | Comments noted. Recommendations are based on evidence of both clinical and cost effectiveness. The Committee heard from the clinical specialists that in clinical practice docetaxel is preferred despite its toxicity because, in their opinion, docetaxel is clinically effective compared with erlotinib. The Committee was also aware that direct evidence comparing erlotinib with docetaxel showed erlotinib to be less clinically effective. |
| Healthcare professional (within NHS) (1) | General | GSTT Lung Cancer CNS Response To NICE Decision To Remove Erlotinib As Second Line Treatment For Patients With Non Small Cell Lung Cancer.<br><br>The lung cancer clinical nurse specialists at Guys and St Thomas Hospital have a run a nurse led clinic for patients receiving TKIs since March 2010. We consent the patients to treatment and then follow the patients through until they have disease progression. Six out of the ten in our current patient group are on second line erlotinib, with a range of treatment from 6 months up to 20 months.<br><br>Our concerns regarding the removal of erlotinib as second line treatment are this:<br><br>In the TAILOR Study it was found that 20% of the patients in the docetaxel arm suffered from grade 3-4 toxic effects with regards to their neutrophil count. Compared to the patients in the erlotinib arm who had no such | Comments noted.<br><br>The Committee noted that although erlotinib was considered to be better tolerated than docetaxel, the health-related quality of life and the cost associated with managing adverse reactions had been accounted for in the cost-effectiveness estimates.<br><br>The Committee considered comments received |

| Role* | Section | Comment | Response |
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| | | events as erlotinib does not affect the bone marrow.<br><br>This in itself would carry a potential cost to the NHS in the terms of visits to accident and emergency departments, IV antibiotics and potential inpatient stays. In the 5 years we have been caring for patients being treated with erlotinib we have admitted one patient due to toxicity and this was due to the patient being embarrassed about location of rash so not reporting it to the nurses.<br><br>Also as nurses are able to effectively and safely care for these patients in a nurse led clinic this allows the clinicians to see more patients who have complex needs. We have seen patient waiting times reduce and patient satisfaction increase in the patients treated in the nurse led clinic. A nurse led clinic is also cost effective. With docetaxel the patients would need to see a clinician, have potentially more hospital visits due to toxicity management and have longer wait times in clinic.<br><br>Patients who have had severe toxicities relating to first line chemotherapy in our experience are extremely reluctant to go on for second line chemotherapy. With some patients becoming very distressed in consultations where this is the next line of treatment suggested. Current practice has been that at the clinicians' discretion these patients have been offered erlotinib as second line. All of the patients are informed that this treatment may only offer a short term holding of their cancer, but they are still keen to try this over further chemotherapy. If NICE remove the option of erlotinib as second line then these patients will effectively be relegated to best supportive care only and a potential poor prognosis. We would suggest that ethically this does not sit right with the principle of beneficence and removes not only the patients' right to choice but also the clinicians' ability to use their expertise in deciding what the right treatment for the right individual is. | during consultation and the additional data on the incidence of febrile neutropenia presented by the Assessment Group in its second addendum. The Committee acknowledged that there was considerable variability, and therefore uncertainty, around the most plausible incidence rate for febrile neutropenia. The Committee concluded that, for all incidence rates of febrile neutropenia suggested during the course of the appraisal (up to 41%), erlotinib did not represent a cost-effective use of NHS resources for the EGFR-TK mutation-negative population (see section 4.3.14 of the final appraisal determination).<br><br>Please note that in the Single Technology Appraisal of erlotinib for the treatment of non-small-cell lung cancer (NICE technology appraisal 162), the guidance clearly stated "erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is,where there is intolerance of or contraindications to docetaxel)." During this appraisal, the Committee heard from the clinical specialists that in clinical practice docetaxel is preferred despite its toxicity because, in their opinion, docetaxel is clinically effective compared with erlotinib. The Committee was also aware that direct evidence comparing erlotinib with docetaxel showed erlotinib to be less clinically effective.<br><br>Although individual choice is important for the NHS |

| Role* | Section | Comment | Response |
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| | | We have recently had a case where a patient was diagnosed with an EGFR WT adenocarcinoma, she struggled to cope with the effects of chemotherapy but managed to complete her treatment. However, this left her fatigued and very adverse to further chemotherapy in the future. Sadly this lady's cancer progressed soon after chemotherapy had finished and the clinician on examining her CT scans felt that the tumour was behaving in the pattern of an EGFR +ve tumour. The only way to disprove the original EGFR test undertaken in another Trust would be to take a new biopsy and repeat the test in GSTT. The lady was not really fit enough to undergo another biopsy and so in discussion with the patient, family and clinicican erltonib was prescribed. So far although we acknowledge it is early days this lady is doing well and has now been able to have a repeat biopsy and we await the result. If erlotinib had been removed by NICE at this point this lady would have been denied treatment that has so far improved her condition.<br><br>Whilst we acknowledge the findings of the TAILOR study and the fact that docetaxel is a much cheaper drug we would request that NICE think very carefully before making any decisions. Treatment options for lung cancer patients are still very limited when compared to treatment options for other cancers. These patients continue to have a poor prognosis and face the stigma of having a cancer that the majority of the general public only associate with heavy smokers.<br><br>Whilst clinical trials are vital for the future treatment of patients with lung cancer we should never lose sight of the patient and their families who have to deal with a cancer that is debilitating and has a devastating effect on both the patient and their families. As nurses it is our duty to speak out for our patients and this is acknowledged in the government white paper which highlighted those patients who had access to a clinical nurse specialist had better access to treatment and tended to cope better with that treatment. It is with all of the above in mind that we feel that erlotinib | and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective (Social Value Judgements - Principles for the development of NICE guidance; principle 5).<br><br>The Committee is required to resist pressure to make decisions that are not in the broad public interest (Social value judgements [SVJ] Principle 12). |

| Role* | Section | Comment | Response |
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| | | should to be offered as second line treatment to patients with non small cell lung cancer. | |
| Healthcare professional (within NHS) (2) | 1 | Feel that you will be denying a very useful treatment i.e second line erlotinib to a vulnerable patient group where they would not otherwise access 2nd line treatment. Assume you will include stable disease as response and not require RECIST criteria. | Comments noted. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective (Social Value Judgements - Principles for the development of NICE guidance; principle 5).<br><br>Please note that in the Single Technology Appraisal of erlotinib for the treatment of non-small-cell lung cancer (NICE technology appraisal 162), the guidance clearly stated “erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel).” During this appraisal, the Committee heard from the clinical specialists that in clinical practice docetaxel is preferred despite its toxicity because, in their opinion, docetaxel is clinically effective compared with erlotinib. The Committee was also aware that direct evidence comparing erlotinib with docetaxel showed erlotinib to be less clinically effective. |
| Healthcare professional (within NHS) (2) | 2 | Feel that you have failed to recognise that the lung cancer community has offered tarceva 2nd line to a wider group of people that we would offer docetaxel to based on clinical experience. the trials have generally younger patients in than my population many of whom are over 70 , even 75 for whom docetaxel would simply be inappropriate and hence the excellent option of erlotinib has been used with good clinical benefit. | Comments noted. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective (Social Value Judgements - Principles for the development of NICE guidance; principle 5). |

| Role* | Section | Comment | Response |
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| | | | Please note that in the Single Technology Appraisal of erlotinib for the treatment of non-small-cell lung cancer (NICE technology appraisal 162), the guidance clearly stated "erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel)." |
| Healthcare professional (within NHS) (2) | 3 | TKIs are very well tolerated and manageable with flexible dosing such that treatment very rarely needs to be stopped completely. | Comment noted. The Committee heard from the clinical specialists that the adverse reactions associated with erlotinib and gefitinib are much less common than those associated with chemotherapy. The Committee recognised the importance of having clinically effective and tolerable treatment options for people with non-small-cell lung cancer that has progressed after prior chemotherapy. |
| Healthcare professional (within NHS) (2) | 4 | The rates of neutropaenic sepsis seen in these Docetaxel studies are not representative of UK experience where almost 20% pts are admitted as we cannot use PEG GCSF for palliative pts. The Tailor study did not use erlotinib as intended as it mandated stopping for grade 3 rash, this in my opinion may have biased the rests as TKIs should be dose reduced in this setting . Erlotinib can be used successfully in pts who do not wish to lose their hair, do not wish to accept the dreadful toxicity we see in the real world with docetaxel for a small clinical response. The grade 1 and 2 toxicity with docetaxel should not be underestimated. Having treated over 100 pts with 2nd line TKI for wild type disease, they fall into 2 groups- those who derive no clinical benefit which you can generally see by 4 weeks and therefore stop and those who have ver durable responses and improvement in quality of life. I have a number of patients for whom this | Comments noted. The Committee considered comments received during consultation and the additional data on the incidence of febrile neutropenia presented by the Assessment Group in its second addendum. The Committee acknowledged that there was considerable variability, and therefore uncertainty, around the most plausible incidence rate for febrile neutropenia. The Committee concluded that, for all incidence rates of febrile neutropenia suggested during the course of the appraisal (up to 41%), erlotinib did not represent a cost-effective use of NHS resources for the EGFR-TK mutation-negative |

| Role* | Section | Comment | Response |
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| | | has been several years. You need to look at the audit experience of the lung cancer community in the UK as they are a different population to those shown in these studies. (with the exception of BR21). | population (see section 4.3.14 of the final appraisal determination).<br><br>The Committee discussed the generalisability of the TAILOR trial to clinical practice in England. For further details, please see section 4.3.10 of the final appraisal determination. |
| Healthcare professional (within NHS) (2) | 5 | Entirely agree with 1st line usage | Comment noted. No action required. |
| Healthcare professional (within NHS) (2) | 6 | SACT data should show the drop in patients accessing 2nd line therapy if the CRG do not recumbent erlotinib or other single agents e.g gemcitabine, vinorelbine or taxol as beyond1st line treatment. | Comment noted. No action required. |
| Healthcare professional (within NHS) (2) | 7 | within one year to look at impact on lung cancer survival in UK | Comment noted. The guidance on these technologies will be considered for review by the Guidance Executive 3 years after final publication. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.<br><br>The length of time between guidance publication and review consideration varies depending on the available evidence for the technology, and knowledge of when ongoing research will be reported. Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations. |

| Role* | Section | Comment | Response |
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| Healthcare professional (within NHS) (3) | General | I write in response to the recent appraisal consultation document regarding the use of erlotinib and gefitinib in lung cancer (non-small cell) rev TA162, TA175. The outcome of the ACD is to recommend that access to erlotinib is denied to those patients that have a negative EGFR test. This outcome follows publication of the results of recent international clinical trials.<br><br>As a specialist in lung cancer treatment I wish to inform you that your appraisal is flawed with respect to the assumptions made in item 4.1.13.<br><br>Our own data was recently reported as an audit of almost 100 patients with EGFR negative non-small cell lung cancer treated with erlotinib post-chemotherapy. This audit shows that judicious, use of erlotinib results in a two-fold improvement in clinical benefit compared to the results of recent clinical trials.<br><br>Docetaxel chemotherapy in England is not administered in the same dosing schedule as reported by the TAILOR study. In addition, the high frequency of intolerable side-effects associated with docetaxel mean that this is an unacceptable treatment. Given that this is a patient group with limited survival, there is no data to support symptom improvement or favourable quality of life with docetaxel.<br><br>The implication of the ACD outcome will be that a high proportion of lung cancer patients will be denied access to life extending second-line treatment, which is a backward step in the treatment of this disease.<br><br>It is my opinion that clinicians, who are very experienced in treating this complex and ultimately deadly disease, should be given the opportunity to select the right treatments for each patient.<br><br>I request the appraisal group reconsider its recommendation. | Comments noted.<br><br>The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the companies' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment Report.<br><br>The Committee discussed the generalisability of the TAILOR trial to clinical practice in England. The Committee also heard from the clinical experts that increasing the frequency of docetaxel infusion had become more common in clinical practice in the preceding 12 months because of the results from the TAILOR trial. The Committee considered that the results of the TAILOR trial were relevant to people in England with non-small-cell lung cancer whose disease had progressed after chemotherapy and whose tumours tested negative for EGFR-TK mutations. The Committee concluded that based on the available evidence and clinical practice in England, erlotinib is less clinically effective than docetaxel in the EGFR-TK mutation-negative population. For further details, please see section 4.3.10 of the final appraisal determination. |

| Role* | Section | Comment | Response |
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| Patient (1) | 1 | There are patients who are EGFR negative who have responded to erlotinib/tarceva | Comment noted. The Committee acknowledged that, despite erlotinib being targeted at the EGFR-TK mutation-positive population, the TAILOR trial indicated that some patients with confirmed EGFR-TK mutation-negative status partially responded to treatment with erlotinib. |
| Patient (1) | 4 | Cost comparisons between docetaxel & erlotinib not robust. Docetaxel more costly to administer due to need to attend hospital, erlotinib taken at home. Patients needing 2nd line treatment are often not strong enough to tolerate chemo. Erlotinib works quickly, so efficacy can be established early on. Lung cancer research pitifully underfunded. Critically ill patients should not be deprived of a drug which can extend quality of life, give time for them and family etc to come to terms with situation. | Comments noted. The Committee noted that although erlotinib was considered to be better tolerated than docetaxel, the health-related quality of life and the cost associated with managing adverse reactions had been accounted for in the cost-effectiveness estimates.<br><br>Recommendations are based on evidence of both clinical and cost effectiveness. The Committee heard from the clinical specialists that in clinical practice docetaxel is preferred despite its toxicity because, in their opinion, docetaxel is clinically effective compared with erlotinib. The Committee was also aware that direct evidence comparing erlotinib with docetaxel showed erlotinib to be less clinically effective. |

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M1 4BT

28 August 2014

**RE: Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175) [ID620]**

Dear Nicole

Thank you for providing the opportunity to comment on the ACD for the above appraisal. We are disappointed that this draft guidance will significantly set-back the treatment of people with Lung Cancer.

The majority of people with this disease are unable to tolerate cytotoxic chemotherapy – erlotinib is their only effective treatment option and can provide two months of additional life[1]. The ERG ICER in this population is £54,686/QALY gained.

We note that this appraisal is expected to continue beyond the time at which NICE's proposals for 'Value Based Assessment' (VBA) will have been implemented.

The QALY multiplier required for approval under the ERG base-case in this group is not substantially above the range quoted in the VBA consultation document (2.7 compared to 2.5). Given the high 'burden of illness' and high 'wider societal impact' associated with Lung Cancer, we would welcome consideration of erlotinib under this new approach. We are committed to finding a long term solution to ensure people with Lung Cancer continue to benefit from erlotinib and would welcome further dialogue on this issue.

Kind Regards,
[redacted]

[redacted]

[redacted]

1. *LRiG ID620 Assessment Report*

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Nicole.Fisher@nice.org.uk

[redacted]

28 August 2014

Dear Ms Fisher

**Re: Multiple Technology Appraisal (MTA) - Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175) - Appraisal Consultation Document 3**

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 30,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who work together to produce joint responses to NICE oncology consultations. We are grateful for the opportunity to consider the above ACD3 and would like to make the following comments.

Our experts note that section 1.3 states:

*'Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-negative.'*

This represents a disappointing reversal of the previous decision, which could remove an established treatment option for patients with non-small cell lung cancer (NSCLC). The decision would be at odds with treatment guidelines from Europe and North America and would limit clinician and patient choice in a disease group where survival in UK patients is amongst the poorest in the western world.

With regard to whether all the evidence has been taken into account and whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence:

Although a range of clinical trial data has been used to support the economic modelling with regard to the costs associated with docetaxel versus erlotinib treatment, it is unarguable that patients enrolled in clinical trials are younger, fitter and have less co-morbidity than typical NSCLC patients, which results in fewer complications of treatment. Furthermore, G-CSF prophylaxis, which was used in all the clinical trials included in the appraisal review, is not recommended by NICE (CG151) and is therefore not available for use. During the consultation observations of clinical specialists, comments from professional organisations and audit

data have consistently stated that real life febrile neutropaenia and hospital admission rates observed with docetaxel treatment are significantly higher than those used for economic modelling by the ERG (a view supported by published literature). Also, that this undoubtedly carries a substantial financial burden to the NHS, in addition to the detrimental effect on quality of life for patients and increased resource-use for overstretched NHS inpatient services.

It is hoped by clinicians and patients alike that erlotinib will not be removed unnecessarily as an option for the second line treatment of advanced EGFR wild type (mutation negative) NSCLC, particularly as docetaxel may not be suitable alternative treatment for all patients and the 'real costs' associated with docetaxel have been underestimated.

Yours sincerely

**Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD 3) on Erlotinib and Gefitinib (post chemotherapy) (rev TA162 and TA175) [ID620].**

**This response is submitted by Roy Castle Lung Cancer Foundation.**

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- We are very disappointed that the Appraisal Committee's third preliminary decision is not to recommend Erlotinib for EGFR mutation negative patients, as a second line therapy. This will limit a therapy option which for some years has been standard clinical practice. This would adversely affect future treatment options for many patients affected by this devastating disease.

- We welcome the recommendations that Erlotinib and Gefitinib are available for use after chemotherapy, in EGFR mutation positive patients, in whom there was a delayed confirmation of EGFR mutation status. The number of patients impacted by these recommendations, however, is extremely small.

- We also welcome the recommendation that Erlotinib is available for use after chemotherapy, in EGFR mutation status unknown, as outlined in Paragraph 1.2. Again, however, the number of patients impacted by this will be very small.

Our comments below are confined to those patients, in whom EGFR mutation status is negative (including those where it is unknown but assumed to be negative). Many of these points were raised in our response to the first ACD, back in February 2014. We do not believe that they have been adequately addressed. The questions we are asked to comment on are as follows:

**i) Has all of the relevant evidence been taken into account?**

We do not have any additional evidence. However, we believe the Committee has failed to take sufficient account of the differences between Docetaxel (the only other anti-cancer drug therapy available in this indication) and Erlotinib, as described in section (ii) below. We also do not think that the Committee has addressed the implications of a false negative EGFR mutation test result.

**ii) Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?**

Comments: No. There are two particular issues.

Comment 1 : We remain deeply concerned that the Appraisal Committee has placed so much emphasis on the TAILOR study, in its assessment, deliberations and decision. Whilst we understand that this represents the only published direct comparison of Docetaxel and Erlotinib, we are very aware that this Italian Study does not reflect practice here in the UK. In the TAILOR Study, Docetaxel is given weekly, whereas in the UK it is administered three weekly. Also, on discussion with clinicians, we note the side effects of Docetaxel reported in this Study are considerably less than we see in practice here (in particular, the febrile neutropenia rate). We are aware that international consensus has concluded that the result of the TAILOR Study should not be used to make decisions about second line therapy in non small cell lung cancer. It is deeply worrying that should this Appraisal Committee decision be finalised, it will ensure a change to standard clinical practice for a significant number of patients, based on a study of questionable relevance to our UK practice,

Comment 2: We believe that the Committee has failed to recognise that Erlotinib is not simply an alternative chemotherapy to Docetaxel, but is a totally different type of therapy, with a very different side effect profile and administration route, making Erlotinib much more acceptable for patients. Whilst we understand NICE's focus on cost effectiveness, surely patient choice and acceptability are also of relevance?

- The side effects of Erlotinib are much less significant than Docetaxel – for which severe neutropenia can be life threatening.
- Many patients comment on the 'toxic' nature of Docetaxel.
- As an oral medication, Erlotinib does not involve repeated day case admissions for iv administration – offering a much greater prospect of treatment closer to home. We are ever mindful that, in the main, this group of patients has a short life expectancy. It is important to ensure that they are able to spend as much time as possible away from the hospital setting.

In this group of patients, at a second line treatment stage, there would be a number, who would reject Docetaxel as a treatment option, based on the side effect profile. Should Erlotinib be denied to this patient group, then no recommended anti-cancer therapy will be available.
Also, for those of borderline fitness for Docetaxel, at present, clinicians can offer oral Erlotinib as a more easily tolerated anti-cancer therapy to this patient group. Should this option be denied, then only the more toxic option will be available.

**iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Comments: No, there are three issues.

Comment 1: The previous Technology Appraisal confined the use of Erlotinib in this indication, to patients who were suitable for Docetaxel therapy. As in (ii) above, this Appraisal Committee decision, if finalised, will remove the option of active second line anti-cancer therapy for these patients. As noted in (ii) above, we are deeply concerned that this decision is being made based on a single study of questionable relevance to UK clinical practice. We therefore do not conclude that assumptions and assessments made in coming to this provisional recommendation are sound.

Comment 2: We note that in EGFR negative patients, unfit for Docetaxel, where the comparator is 'best supportive care', as with the original appraisal, it is concluded that Erlotinib is not deemed cost effective. We take this opportunity to remind the Appraisal Committee that, for this patient group, Erlotinib remains the only active anti-cancer therapy option and with this decision, access will continue to be denied.

Comment 3: Across the globe, Erlotinib has become a standard therapy option, in second line, for patients with non small cell lung cancer. Clearly, we do not wish to see the NHS in England deprive lung cancer patients of therapies routinely available elsewhere. Changing the current standard of care for English patients will not only have a negative impact on patients but, will limit English participation in clinical research in this patient group, amongst whom, there is still much unmet need.

**The patient's viewpoint:**

Finally, as a lung cancer charity, we have contact with patients through our social media outlets and on line forums. As indicated in our response to ACD1, the public announcement of that particular Appraisal Committee Document provoked some of the most comments on any single topic, we have seen. They serve as a reminder of the impact of a negative decision on real patients and their families.

- *"My mum has been taking Tarceva as a second line treatment since June and she is stable and enjoying life again..... . Apparently, you can, it seems put a price on life... . Mum nearly lost all her will to live. ... Tarceva is saving her life."*

- *"..... I have been on Tarceva since August 22 2013 and although I am not EGFR positive, it seems to be working, at least keeping it at bay. ....."*

- *"I cannot believe that a decision like this can be made. Yet, if you live in Scotland, it won't affect you. If this is carried out, it will seem like a death sentence when chemo isn't an option. ....."*

The sheer disappointment expressed after ACD 1 was replaced by many positive comments, on the announcement of ACD 2, with a positive recommendation in EGFR mutation status negative patients. Sadly, this ACD 3, has reverted to the negativity of ACD 1. This has been a frustrating appraisal process for those lung cancer patients, who have been following its progress.

We welcome the ongoing nature of the appraisal process and hope that the Appraisal Committee will re-consider their decision at the earliest opportunity and also include, within its recommendations, that Erlotinib is also available within the NHS, in the second line setting, as a therapy option for EGFR mutation negative patients.

**Jesme Fox**
**Medical Director**
**Roy Castle Lung Cancer Foundation**
**August 2014**

Ms Lori Farrar
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21 August 2015

**Re: NICE technology appraisal - Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175) [ID620]**

Dear Lori,

Thank you for your letter of 24th July 2015 inviting us to comment on the NICE position statement "Pharmaceutical Price Regulation Scheme 2014 – implications for NICE".

We continue to believe it is unfair to disregard the consideration of PPRS payments within the appraisal process and are deeply disappointed that the conclusion reached by NICE is that "the 2014 PPRS payment mechanism should not be regarded as a relevant consideration in its assessment of the cost-effectiveness of branded medicines".

We acknowledge that there are significant and complex challenges to implementing a workable solution; however it is discouraging that attempts to identify a solution have not been more vigorously pursued.

Erlotinib is the only active treatment that is available for people with EGFR mutant negative NSCLC, who are not fit enough to tolerate cytotoxic chemotherapy. Compared to best supportive care, erlotinib can provide improved survival and quality of life, both of which are important to people with extremely short life expectancy.

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While the branded drugs spend within the PPRS scheme remains above the defined growth levels there is no additional cost to the healthcare system of providing both clinicians and patients the choice to receive erlotinib. Patients who have extremely limited treatment options could therefore benefit from a long established therapy such as erlotinib, without increasing the branded drug spend in the NHS.

We ask NICE to consider a pragmatic solution where the Committee issue positive guidance conditional upon the following points:

- Roche remain within the 2014 PPRS scheme
- The spend level within the 2014 PPRS scheme remains above the agreed growth levels
- Guidance is reviewed at the commencement of the 2019 PPRS scheme

Yours sincerely,

[redacted], [redacted]

Roche Products Limited