Appendix G - professional organisation statement

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] **submitting comments on behalf of:**

Name of your organisation:

NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by [redacted]

Are you (tick all that apply):

- **a specialist in the treatment of people with the condition for which NICE is considering this technology?**

- **a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?**

- **an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?**

- **other?**

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The current standard first line treatment for patients with known EGFR mutant positive NSCLC in the UK is an oral EGFR tyrosine kinase inhibitor (TKI).

However there is considerable national variation in the speed of turnaround of EGFR mutation testing and a clinical decision to treat must be made in some instances before the EGFR mutation result is known. In these cases if an EGFR mutation were detected after the initiation of first line systemic chemotherapy, an oral EGFR TKI would be considered as second or subsequent line of treatment.

Clinicians agree that EGFR TKIs are an effective treatment, but there is debate about which agent provides the best balance between improvement in progression free survival (PFS) and overall survival (OS), and toxicity. Currently available EGFR TKIs include erlotinib and gefitinib. Both are NICE approved and in routine use, with clinicians making a choice between them on the basis of the patient's individual clinical circumstances and efficacy/toxicity preferences.

At present afatinib could also be considered in cases where patients have already received a reversible EGFR TKI for a duration of greater than 12 weeks and systemic doublet chemotherapy.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

All NSCLC patients with a proven sensitising EGFR mutation should be offered an EGFR TKI. They should be considered even in those with poorer performance status.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Afatinib should be prescribed and monitored under the care of a consultant oncologist.

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

In July 2013 afatinib was approved by the U.S. Food and Drug Administration (FDA), and in the same month a positive opinion was issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA).

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The findings of the LUX Lung 3 (afatinib versus cisplatin/pemetrexed for first line treatment in EGFR mutant positive adenocarcinoma of lung) has been published online (jco.ascopubs.org, July 1, 2013) and show that the study met its primary endpoint with and improved PFS of 11.1 vs. 6.9 months (p=0.0004). In the group of patients harbouring exon 19 deletions or L858R mutations in the EGFR gene, and therefore comparable with currently reported studies using other EGFR TKIs, the median PFS of those treated with afatinib was 13.6 months. There was also improved overall response rate (ORR) (56.1 vs 22%, p=0.001) and quality of life, but OS was not improved.

The results of LUX Lung 6 (afatinib vs cisplatin/gemcitabine for first line treatment in EGFR mutant positive Asian patients with NSCLC) has been reported in abstract at the ASCO 2013 (JCO 31, 2013, suppl; abstr 8016) and has also demonstrated an improved PFS of 11.1 vs. 5.6 months (p>0.0001).

Guidance is available from the NCCN on the use of EGFR TKIs for NSCLC patients with EGFR mutation positive tumours (NCCN Guidelines Version 2.2013 Non-Small Cell Lung Cancer). In summary, first-line use of an EGFR TKI is advocated, or 'switch maintenance' for those in whom an EGFR mutation is discovered during first line therapy with chemotherapy. That advice is in line with current UK practice.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There are no reported direct head-to-head comparisons of afatinib versus the other licensed and NICE approved EGFR TKIs (erlotinib and gefitinib). However the LUX Lung 7 study (afatinib versus gefitinib for first line treatment in EGFR mutant positive

NSCLC) should provide useful information about this when complete. The study is however still in its recruitment phase.

Direct cross comparison between studies of EGFR TKIs is not possible. However it seems that response rates and durability vary modestly across EGFR TKIs and that improved efficacy tends to come at the cost of increased 'class-effect' toxicities.

Published quality of life data from LUX Lung 3 has shown better control of cancer related symptoms including cough and dyspnoea using afatinib compared to doublet chemotherapy with cisplatin and pemetrexed, Treatment related symptoms including fatigue and nausea were reported as better with afatinib but diarrhoea, dysphagia and sore mouth were worse.

In summary, from the available clinical trial evidence there appear to be noticeable but overlapping differences in both toxicity and efficacy between EGFR TKIs and afatinib. These differences are borne out in clinical practice. It is therefore widely held amongst non-surgical oncologists that afatinib should be considered as an alternative drug alongside erlotinib and aftatinib in order to widen the choices available to physicians and patients in this setting.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

All NSCLC patients with an activating EGFR mutation are candidates for afatinib, regardless of histological subtype of tumour.

Response and toxicity assessment should be made as per local institutional policy for the currently available EGFR TKIs. As for other EGFR TKIs caution should be observed when discontinuing therapy. The subsequent line of therapy, if appropriate, should ideally commence immediately upon discontinuation of EGFR TKI in order to reduce the incidence of tumour flare.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The LUX Lung suite of clinical trials has been performed in appropriate populations and have asked 'real world' questions that are relevant to current UK clinical practice.

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The LUX Lung 3 trial has the greatest bearing on the proposed appraisal of afatinib. In that study afatinib was randomised against the combination of pemetrexed and cisplatin, which is the current gold standard chemotherapy treatment for patients with advanced non-squamous carcinoma of the lung, This was not the case for either of the analogous studies for the gefitinib (IPASS), or erlotinib (EURTAC) as at the time of their inception pemetrexed had not yet become the standard of care in this setting.

The primary and secondary endpoints for the LUX Lung 3 study were appropriately assessed by independent review. The study was well conducted and adequately powered.

In the LUX Lung 3 study a wide range of different EGFR mutations were detected, and there was planned stratification according to the type of EGFR mutation observed (exon 19 deletion, L858R, or other). This allowed an analysis of outcome according to mutation type, and more accurate comparison with trials of comparator drugs. For example, in the EURTAC study only exon 19 deletions and L858R mutations were studied, and whilst a panel of 29 genetic abnormalities were detected in the IPASS study, the published OS results make reference only to those with exon 19 deletions and L858R mutations.

The observed PFS for afatinib of 13.6 months for those with exon 19 deletions or L858R mutations provides a favourable comparison with trials of competitor drugs, whilst the PFS of 6.7 months for the control arm is in line with results previously reported for the cisplatin and pemetrexed combination (5.3 months median, 95% confidence interval 4.8 – 5.7 months).

The afatinib related toxicities observed in the LUX Lung studies can be considered overlapping in range, but distinct in grade in comparison to its competitors.

Therefore in summary the addition afatinib to the range of drugs at individual patients' disposal for the treatment of EGFR mutation positive NSCLC is likely to be of benefit.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Side effects of afatinib are consistent with the class effects observed from other EGFR TKIs and are well described. Whilst toxicities may be significant, with careful management they can be effectively managed. Quality of life for patients receiving EGFR TKIs such as afatinib is generally better than that observed in patients receiving systemic chemotherapy.

Any additional sources of evidence

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Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None available.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Implementation of the NICE technology guidance for afatinib would provide greater choice for patients with this condition with respect to the trade off between efficacy and toxicity.

No additional education or training for NHS staff would be needed above that which is appropriate in prescribing other available EGFR TKIs. No additional resources would be required.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

No

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

No

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

N/A