Clinical Expert Submission Template

Thank you for agreeing to give us a personal statement on your 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. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

What is the 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 in 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?

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?

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)?

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?

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.

Non small cell lung cancer is the most common variant of lung cancer and as most patients present with advanced disease, carries a poor prognosis. Many of the patients are of poor performance status initially and this often recurs on relapse precluding them from having further treatment. Very few patients are well enough to receive second line chemotherapy. Thus further active systemic treatment is not possible for many of these patients at this stage. Erlotinib therapy can be offered to patients with poorer performance status (2 or more) and used for relapsed patients, or those with chemoresistant tumours, who may benefit as much as those with better performance at this stage. There is no evidence of any benefit when this drug is added to chemotherapy regimes.

There is evidence from clinical trials that female patients, who are lifelong non-smokers and of East Asian origins with adenocarcinoma or broncho-alveolar cells carcinoma origins show the greatest benefits.

The treatment should be given in specialist settings, but as it is an oral targeted therapy (EGFR tyrosine kinase inhibitor) and not a cytotoxic agent, it requires less monitoring, less specialist pharmacy time and could be given through a clinic in a local cancer unit, rather than a cancer centre, which would be convenient for a patient in this stage of their disease. It is a daily tablet and easy for patients to take.

Pemetrexed had been studied in the second line setting after failure on platinum containing regimes. Currently Docetaxel is often used in this situation and this is in the current NICE guidance for treatment of Non Small Cell Lung Cancer. Docetaxel has a significantly higher toxicity of both grade 4 neutropeania and hospitalisation for neutropaenic sepsis than pemetrexed. Erlotinib could also be used as an alternative to both these drugs. There is efficacy in this setting and as it is not myelosuppressive, and being an oral agent can be given more easily to patients with less use of hospital time.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK. Is the technology 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 use?

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.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. 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?

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?

At present there is very little to offer patients who have relapsed after one or two lines of chemotherapy. Presently patients with all forms of NSCLC have been given these drugs in the expanded access trials, and it has not been restricted to the patients who are likely to see the greatest benefits. Theoretically patients with tumours with highest rates of expression of EGFR or mutations thereof, would be expected to respond best, but at present these are not measured routinely. Data on the value of such tests are

not yet clear, and the molecular markers tested have not been shown to reliably predict response.

Currently practice in this country does reflect the results of trials, in that patients are generally offered this treatment when they relapse usually after second line chemotherapy. Some patients will not be fit enough to receive further cytotoxic therapy after first line treatment and evidence suggests that erlotinib as effective as cytotoxic chemotherapy.

The most important outcomes from the trials are that quality of life for these patients is improved, with improvement of breathlessness, cough and pain, and there is a small survival benefit with median survival increased by two to four months. This is similar to the benefits of many cytoxic drugs used in advanced cancers of other types. An increase in progression free survival is also observed, as is survival at one year. In the studies these results are obtained when the drug is given to all types of non-small cell lung cancer, better results would be expected in patients from groups with highest response rates, namely non-smoking females with adenocarcinomas. The pharmaco-kinetics of the drug suggest that it is more rapidly excreted in smokers which will affect efficacy.

Most patients develop on acneiform skin rash, which may require treatment. It is more disfiguring for women than men. Diarrhoea is another common side effect in patients and may be troublesome. These side effects may require a dose reduction, but rarely result in cessation of treatment.

Chest physicians will need to be at hand for this therapy as there is a suggestion in the literature that the development of interstitial lung disease may be a complication of this type of targeted therapy, though the incidence is low and the greatest evidence for this complication is from the Japanese literature, particularly with a related EGFR inhibitor gefitanib. This side effect will need to be monitored if the drug is more widely used. It has been found to be life threatening during use of these drugs in Japan, but risk of this side effect is much smaller than the incidence of neutropaenic sepsis for instance with second line chemotherapy. At the present time the risk of this side effect might suggest that any patients with evidence of Interstitial Lung Disease on their CT scan should not receive this form of therapy. However the clinical benefit of erlotinib therapy far outweighs the risk.

I have limited knowledge of pemetrexed, and I do not feel I am able to comment on the relative benefits of this drug compared to other available second line chemotherapy in non- small cell lung cancer.

Any additional sources of evidence?

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.

These data are available but I do not have them to hand in sufficient detail to help in this appraisal. I have seen these data presented at meetings of Thoracic Oncology.

Implementation issues

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)?

The NHS is required by the Department of Health and 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 Welsh Assembly Government to vary this direction.

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

If patients were now able to receive more second or third line treatment, with an improvement in survival, more patients would be attending clinics for follow-up, but use of hospital resources would be less than with cytotoxic chemotherapy in this situation. Erlotinib is not myelosuppressive and haematological monitoring is not necessary. Imaging would be used to assess disease stability or progression. Education and training in dealing with the side effects would be necessary, but this is relatively straightforward.