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Single Technology Appraisal (STA)

Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer [ID729]

Thank you for agreeing to give us a 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.

Please do not exceed the 8-page limit.

About you

Your name: Martin Forster

Name of your organisation: UCLH

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- 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.)? **No**
- other? (please specify) **Member of NCRI Lung Clinical Studies Group**

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

How is the condition currently treated in the NHS?
Currently in the UK patients with ALK-driven NSCLC who are fit enough to receive therapy are initially treated with platinum-based combination chemotherapy, usually platinum-pemetrexed. On progression, they may be eligible to receive crizotinib via the Cancer Drugs Fund (CDF), which leads to further disease control for the majority of patients but unfortunately all will progress (median PFS 7.7 months).

On progression through crizotinib therapy (position of this STA submission) the current treatment options are limited and there is a significant unmet clinical need. A proportion of patients who remain fit, ~30%, may receive further chemotherapy with docetaxel, which offers a response rate of ~10% and median PFS of 3-4 months, but the majority of patients will receive no further active anti-cancer therapy, managed with best support care only.

Is there significant geographical variation in current practice?
The first line management of patients fit enough for active therapy with a platinum-based combination will vary little across the country. ALK testing may be variable across the country but I believe it is now being performed in the majority of cancer centres and units. Within England, access to crizotinib as second line therapy is universal via the CDF and so there should not be large variation in current practice. Use of 3rd line therapy with docetaxel will vary to a degree across centres, but I believe this will be driven more by patient fitness and co-morbidities than geographical variants.

Are there differences of opinion between professionals as to what current practice should be?
Use of docetaxel in relapsed NSCLC is well established. It has a limited role with low response rates (~10%) and marginal impact on PFS and OS. It causes significant side effects and so it is only used in a small proportion of patients fit to receive it. I do not think there is a large difference of opinion on this.

There is however an ongoing debate about whether a proportion of patients on crizotinib who develop progression limited to only one or a few sites may benefit from localised therapy to these progressing sites with continuation of crizotinib. This practice may vary across clinicians.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
As mentioned above, for fit patients docetaxel would be the main alternative therapy to ceritinib, once there is clinically relevant progression on crizotinib. For patients unfit for docetaxel there is not current alternative in addition to best supportive care.

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The activity of docetaxel is limited (ORR <10% and marginal impact on mOS) and it is associated with significant toxicity within this patient population. Ceritinib has numerous overwhelming advantages, both in the likelihood and duration of benefit (as submitted within this STA, ORR >40%, disease control rates of ~75%, duration of response >8 months and median PFS ~6 months) and the limited number of clinically relevant side effects. The only potential benefit of docetaxel over ceritinib would be cost based.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Other than general overall fitness, which is usually associated with outcome, there are no established clinical prognostic factors within this ALK-positive patient population. There has been work looking at whether certain patterns of progression on crizotinib are associated with different prognosis. In other forms of NSCLC, patients with brain metastases have a worse prognosis, however, of particular interest, all patients including those with brain metastases appear to gain similar benefit from ceritinib.

There has also been a lot of work over recent years investigating mechanisms of resistance to crizotinib. There is significant understanding about the biological mechanisms of resistance to crizotinib and the majority (although not all) remain sensitive to ceritinib, with no clear clinical sub-populations who do particularly well or badly. Currently, there is also inadequate biological understanding to differentiate particular groups who should / should not receive ceritinib post crizotinib.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
There are no data suggesting differential toxicity to ceritinib.

As mentioned above, there is increasing understanding of the underlying biological mechanisms of resistance to crizotinib but these do not currently define patient subgroups that should be managed differently. Preclinical and translational data show that most mechanisms of resistance to crizotinib appear to retain sensitivity to ceritinib, although some secondary ALK mutations may be less sensitive.

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)?
Treatment should be prescribed by appropriately trained oncologists, supported by a chemotherapy team including appropriately trained nurses and pharmacists. Prescription, delivery and patient management are not excessively complex and could be delivered through smaller cancer units as well as larger cancer centres.

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?

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Ceritinib is not currently available in England. Previously it was available through clinical trials and then an expanded access program but since licensing approval it has not been available.

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.
ASCO guidelines (most recently updated Aug 2015) recommend ceritinib for patients with ALK driven disease progressing after crizotinib. The guidelines are based on the same data presented within this STA and have been considered by a lung expert reference group and presented appropriately.

Current ESMO guidelines are older and predate the presentation of clinical data with ceritinib.

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?
The increased understanding of the biology underlying lung cancer has led to the recognition that a proportion of tumours are driven by particular molecular drivers. These include ALK translocations in 3-5% of UK NSCLC patients. The co-development of drugs able to inhibit growth of these tumours is revolutionising the management of lung cancer and driving a patient-centred precision medicine approach.

For patients with ALK-driven disease, crizotinib has been shown to be a more effective management than chemotherapy and crizotinib is currently available as second line therapy through the CDF. There are data demonstrating the benefits of crizotinib over chemotherapy as first line therapy for ALK-driven NSCLC and in the future it is likely this will become a standard of care here in the UK, as it is already elsewhere around the world.

However, patients will progress on crizotinib (whether as first or second line therapy) and the current alternatives are chemotherapy or best supportive care (BSC). Within this STA, the standard therapy is either docetaxel (for fit patients) or best supportive care for anyone more frail (the majority). As outlined above, docetaxel, whilst a recognised standard therapy, only helps a minority of patients and is associated with significant side effects. The data presented within this technology appraisal demonstrate that ceritinib leads to tumour regression for a clinically meaningful duration for the majority of patients with ALK-driven NSCLC after crizotinib therapy and if it becomes available ceritinib I believe it will be used in almost all settings in preference to currently available therapies. It is an oral medication and therefore will be easier to deliver than docetaxel and requires less supportive medication. Some caution will be required about concomitant medication but this is not

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overly complex and very manageable. For patients too frail for docetaxel their only option is best supportive care and they therefore represent a significant unmet clinical need and a powerful therapy such as ceritinib has particular importance for them.

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 patients will need to have had previous ALK testing to be eligible for this technology, but given that patients will have already received crizotinib this will not require further analysis. Whilst re-biopsy and further tissue is of academic interest it will NOT be required for eligibility for the technology. As mentioned above, I do not think that there is adequate clinical evidence at this point to suggest particular molecular subpopulations that do not gain benefit from ceritinib in this setting. Therefore I do not think specific additional testing is required to guide patient selection. Patients need to be monitored on treatment and treatment should be stopped when clinically relevant disease progression has occurred.

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?
The patient characteristics within these STA-submitted trials reflect accurately the ALK-driven UK population.

ALK translocation is very much more frequent in lung adenocarcinoma than other NSCLC sub-populations and is very uncommon to co-occur with EGFR mutation. In addition, patients with ALK-driven NSCLC tend to be younger than other 'non mutation-driven' NSCLC and are more likely to be non smokers or light ex-smokers. These characteristics are described within these studies and remain consistent with UK population.

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?
In the analysis of randomised trials in molecular driven lung cancers such as EGFR mutation and ALK translocation driven NSCLC it is recognised that there is a high degree of cross-over, meaning that overall survival is no longer the most relevant outcome. However, I believe that Progression Free Survival has been demonstrated to reliably predict for improved overall survival within molecular patient sub-populations and I therefore feel this is the most relevant outcome. Overall Response Rate (ORR) and Duration of Response are also of relevance, although I am not so certain that ORR predicts longer-term outcomes as reliably. Quality of life also continues to be an important outcome.

All these outcomes are available within this STA based on 2 single arm studies.

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Both demonstrate very impressive outcomes with mPFS of 5.7 and 6.7 months in ASCEND-1 and ASCEND-2 trials respectively.

Overall response rates and duration of response in both studies were also dramatic at 39% and 56% and 9.7 and 8.3 months respectively. These data are truely outstanding and represent a huge benefit for these patients, who having progressed on crizotinib have a significant unmet need with limited available effective treatment options.

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?
The toxicities described within these trials accurately reflect clinical experience with these drugs. As described in the STA submission ceritinib is generally very well tolerated and side effects are manageable. A proportion of patients (~40%) do require a dose interruption or dose modification but rarely does treatment require permanently stopping.

Patient reported outcomes confirm a good improvement in quality of life.

Equality and Diversity

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

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

I do not think that this appraisal will lead to any of the equality and diversity concerns outlined above. As all patients will have had crizotinib even possible variability in ALK testing across the UK will not directly influence availability of the submitted technology.

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.

I am not aware of other sources of data that needs to be reviewed in addition.

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)?

I do not believe there would be a big impact on clinical services should this treatment be approved. As this patient population only represents 3-5% of NSCLC, the patient numbers in any single practice will be small and therefore impact on the whole service limited. A degree of training would be required for oncology staff but this would not be extensive.

Patients with ALK-driven NSCLC tend to be young (median age in both studies was early 50s) and therefore increased survival with high degree of symptom control and manageable toxicities may lead to increased ability for these patients to continue work and other societal contributions, in addition to the benefit to the patients themselves.