National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor [ID1468]

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.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Takeda	The draft remit does not accurately reflect the proposed marketing authorisation which is: *"Brigatinib is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor"*. However, Takeda would like to note that this proposed wording is subject to potential change, up until the date of anticipated CHMP opinion. In light of the above, we would suggest that the title of this appraisal should be changed from *"Brigatinib for untreated ALK-positive metastatic non-small-cell lung cancer [ID1468]"* to *"Brigatinib for ALK-positive advanced non-small-cell lung cancer previously untreated with an ALK inhibitor [ID1468]"*. This would ensure that the title of the appraisal accurately reflects the proposed marketing authorisation for brigatinib and would also be consistent with the text in the technology section of the draft scope.	Thank you for your comment. The scope title has been amended to more accurately reflect the marketing authorisation.
Timing Issues	Takeda	Brigatinib has demonstrated considerable superiority over crizotinib in the ALTA-1L clinical trial. Marketing authorisation for this indication is expected to	Thank you for your comment. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		be received [redacted] and Takeda wish to provide access for patients in the UK at the earliest possible opportunity.	
Additional comments on the draft remit	Takeda	None	Thank you for your comment. No change to scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Takeda	We agree with the accuracy of the background information. For completeness, we would like to add that the most recent 2018 National Lung Cancer Audit data on NSCLC estimates that 1.2% of patients received targeted therapies for ALK mutations. Therefore, in a population of 39,205 cases of NSCLC in England & Wales, the incidence of patients with ALK mutations would be approximately 470 patients.	Thank you for your comment. This section of the scope aims to provide a brief overview of the background for the appraisal. Additional details may be considered by the committee at the time of the appraisal, if appropriate. No change to scope required.
The technology/ intervention	Takeda	Yes.	Thank you for your comment. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Takeda	Please modify the wording to "Adults with ALK positive **advanced** NSCLC that has not been previously treated with an ALK inhibitor". There are no groups within this population that we think should be considered separately.	Thank you for your comment. This section of the scope has been amended.
Comparators	Takeda	We request the removal of ceritinib as a comparator because its negligible usage shows that it is not a standard treatment currently used in this setting in the NHS. This has also been validated with clinical experts who confirm that the only currently used frontline ALK inhibitors in the UK are alectinib and crizotinib. Hence, we do not regard ceritinib as a relevant comparator for brigatinib in this appraisal. The rationale for this is explained further below. The dynamics within the ALK-positive advanced NSCLC market have changed significantly since alectinib was recommended by NICE for previously untreated patients (positive FAD issued in June 2018 – TA536). Alectinib is now very firmly established as the standard of care for new patients in this setting and the use of crizotinib in new patients has declined dramatically. This was recognised by NHS England during the appraisal of brigatinib in the post-crizotinib setting (TA571): *"Alectinib is the main 1st line option currently used in NHS England for newly diagnosed patients on account of its better tolerability"* (see page 72 of the Committee papers). This is also reflected in NICE's Resource Impact Report for TA536 (published in August 2018), where it states that uptake of alectinib is estimated to reach 90% of eligible patients by 2019/20 (NHS England estimate). Therefore, we regard alectinib as the most relevant comparator for brigatinib in this appraisal. Despite being recommended by NICE in January 2018, the use of ceritinib in the first-line setting has always been extremely limited. With alectinib dominant at first-line (74% market share on a moving quarterly basis in December 2019, and rising. Source: Medimix LiveTracker, December 2019),	Thank you for your comment. The scope reflects published guidance. Ceritinib has been retained because there may be some patients (albeit few) who use it in clinical practice. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		the use of ceritinib as a first-line ALK inhibitor is now negligible (1% market share. Source: Medimix LiveTracker, December 2019). Therefore, we regard ceritinib as an irrelevant comparator for this appraisal and would suggest it should not be included in the final scope. Based on its continuing use in some patients (17% market share on a moving quarterly basis in December 2019. Source: Medimix LiveTracker, December 2019), crizotinib remains a relevant comparator for this appraisal. NICE guidance recommends crizotinib for untreated ALK-positive advanced NSCLC (TA406) and for the treatment of patients with ALK-positive advanced NSCLC who have received prior chemotherapy only (TA422).	
Outcomes	Takeda	As per our comments on the Company Decision Problem form submitted on September 2019, we request the addition of central nervous system (CNS) efficacy (intracranial PFS, intracranial response).	Thank you for your comment. CNS efficacy outcomes (intracranial PFS, intracranial response) would be covered by 'progression-free survival' and 'response rates' in the scope. No change to scope required.
Economic analysis	Takeda	We note the comment in the draft scope about cost-comparison as a potential approach – we consider the comparison of brigatinib with alectinib to meet the requirements specified by NICE for a simple cost-comparison. Therefore, a cost-comparison analysis will be presented in our base case for brigatinib vs. alectinib. Based on the results from the ALTA-1L trial of brigatinib vs. crizotinib, and some indirect treatment comparisons, we believe brigatinib is likely to provide	Thank you for your comment. Scope amended to reflect the fact that ALK testing is now routine in clinical practice.

Section	Consultee/ Commentator	Comments [sic]	Action
		similar or greater health benefits than alectinib in the first-line setting. This view is supported by clinical experts who regard the results seen to date in the ALTA-1L trial as similar to those seen in the ALEX trial of alectinib vs. crizotinib (PFS per IRC: HR = 0.49 [95% CI, 0.35 to 0.68] at a median follow-up 24.9 months in ALTA-1L; HR = 0.50 [95% CI, 0.36 to 0.70] at a median follow-up of 18.6 months in ALEX). Hence, from the perspective of the NHS, we believe cost-comparison could provide an appropriate framework in which to compare brigatinib with alectinib, and we would encourage NICE to accept such an analysis. We also note the statement in the draft scope re ALK testing and would make two comments: firstly, the introduction of brigatinib as a first-line ALK inhibitor would not lead to more people being tested for ALK as such testing is already part of routine clinical practice in NSCLC (i.e. ALK testing is already necessary prior to the first-line use of the existing ALK inhibitors); and secondly, the cost of ALK testing is the same regardless of which ALK inhibitor is prescribed. In the economic modelling, we will include the same cost for ALK testing for brigatinib and the comparators and will provide a sensitivity analysis without these costs.	
Equality and Diversity	Takeda	We have not identified any equality issues.	Thank you for your comment. No change to scope required.
Other considerations	Takeda	No additional suggestions.	Thank you for your comment. No change to scope required.
Innovation	Takeda	Brigatinib is a next-generation ALK inhibitor, with broad coverage against several clinically relevant ALK mutations.	Thank you for your comment. Innovation

Section	Consultee/ Commentator	Comments [sic]	Action
		In a large multicentre, international Phase III study (ALTA-1L), brigatinib has shown significantly greater efficacy than crizotinib in terms of progression-free survival (PFS), intracranial PFS, objective response rate (ORR) and intracranial response, in patients with advanced ALK-positive NSCLC who have not previously received an ALK inhibitor. As a once-daily, single tablet that can be taken with or without food, brigatinib offers significant patient convenience advantages over the other ALK-inhibitors which require either twice-daily dosing (alectinib and crizotinib), or multiple capsules to be taken at one time (alectinib and ceritinib) or must be taken with food (alectinib and ceritinib).	will be considered by the appraisal committee when formulating its recommendations. The company will have opportunity to provide evidence on the innovative nature of its product in its submission. No change to scope required.
Questions for consultation	Takeda	**Q. Have all relevant comparators for brigatinib been included in the scope?** A. Yes. As mentioned above, we regard alectinib as the most relevant comparator for brigatinib in this appraisal, while crizotinib is also of some relevance but diminishing. Due to lack of use in the first-line setting (1% market share), we do not regard ceritinib as a relevant comparator and would suggest it should not be included in the final scope. **Q. Which treatments are considered to be established clinical practice in the NHS for untreated ALK-positive metastatic NSCLC?** A. Clinical opinion is that essentially all new patients in the UK with untreated ALK-positive advanced NSCLC are now receiving alectinib as first-line treatment. Crizotinib continues to be used in a minority of patients, while ceritinib use is negligible. This is reflected in the market share data summarised above. **Q. Are the outcomes listed appropriate?** A. In general, yes. We request the addition of (CNS) efficacy (intracranial PFS, intracranial response).	Thank you for your comment. Please see above response in the 'comparators' section of this comments table. Thank you for your comment. No change to scope required. Thank you for your comment. Please see above response in the

Section	Consultee/ Commentator	Comments [sic]	Action
		Q. Are there any subgroups of people in whom brigatinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? A. No.	'outcomes' section of this comments table.
		Q. Where do you consider brigatinib will fit into the existing NICE pathway, Lung cancer? A. In line with the proposed marketing authorisation, brigatinib would be used as an alternative to alectinib (predominantly) or crizotinib in adult patients with ALK-positive advanced NSCLC previously untreated with an ALK inhibitor.	Thank you for your comment. No change to scope required.
		Q: 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 the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: A: No to all of the questions asked here.	Thank you for your comment. No change to scope required.
		Q: Do you consider brigatinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A: Brigatinib is a next-generation ALK inhibitor, with broad coverage against several clinically relevant ALK mutations. In a large multicentre, international Phase III study (ALTA-1L), brigatinib has shown significantly greater efficacy than crizotinib in terms of progression-free survival (PFS), intracranial PFS, objective response rate (ORR) and	Thank you for your comment. Please see above response in the 'innovation' section of this comments table.

Section	Consultee/ Commentator	Comments [sic]	Action
		intracranial response, in patients with advanced ALK-positive NSCLC who have not previously received an ALK inhibitor As the only ALK inhibitor available as a once-daily, single tablet that can be taken with or without food, brigatinib has significant patient convenience advantages over the other front line ALK-inhibitors which require either twice-daily dosing (alectinib and crizotinib), or multiple capsules to be taken at one time (alectinib and ceritinib) or must be taken with food (alectinib and ceritinib). **Q: Do you consider that the use of brigatinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** A: Brigatinib has a more convenient dosing regimen compared to other ALK inhibitors (see above) and offers significant benefits to patients and carers that may not be reflected fully in the QALY calculation. **Q: Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** A: In our submission to NICE, Takeda will explain what these advantages are and how they can benefit patients and carers. We would encourage NICE and the Appraisal Committee to seek input from clinical experts and Consultees such as Patient/carer groups and Professional Groups in this area. **Q: To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**	Thank you for your comment. No change to scope required. Thank you for your comment. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		A: None expected. It would be used in place of other ALK inhibitors (predominantly alectinib). **Q: Would it be appropriate to use the cost comparison methodology for this topic?** A: Yes, as discussed above, but only in comparison to alectinib. Given the similarities in the clinical data, we believe a cost-comparison could provide an appropriate framework in which to compare brigatinib with alectinib, and we would encourage NICE to consider such an analysis. **Q: Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** A: Yes, as discussed above, brigatinib is similar to (at least as good as) alectinib in terms of clinical efficacy and resource use. As described above, brigatinib has demonstrated considerable clinical superiority over crizotinib in the ALTA-1L clinical trial. Brigatinib offers significant patient convenience advantages over the other currently available ALK-inhibitors in this setting. **Q: Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** A: Yes. **Q: Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** A: No.	Thank you for your comment. No change to scope required. Thank you for your comment. No change to scope required. Thank you for your comment. No change to scope required. Thank you for your comment. No change to scope required. Thank you for your comment. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Takeda	None.	Thank you for your comment. No change to scope required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None