National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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	Yes	Comment noted. No action taken.
	BTOG-NCRI-ACP-RCP	Agree	Comment noted. No action taken.
Timing Issues	Takeda	As any cancer medicine.	Comment noted. No action taken.
	BTOG-NCRI-ACP-RCP	Appraisal as per standard pathway	Comment noted. No action taken.
	Takeda	No.	Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	BTOG-NCRI-ACP-RCP	No	Comment noted. No action taken.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Takeda	Lung cancer falls into two main histological categories: non-small-cell lung cancers (NSCLC), which account for 88% of all lung cancers (Royal College of Physicians. National Lung Cancer Audit 2016 (for the audit period of 2015). Published January 2017), and small-cell lung cancers. NSCLC may be grouped by tumour histology into squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, with the latter two being collectively referred to as 'non-squamous' lung cancer. Anaplastic lymphoma kinase (ALK) fusion genes are chromosomal alterations that occur between the tyrosine kinase portion of the ALK gene and other genes. They are believed to be involved in the growth of tumours. ALK translocation can occur in NSCLC of any histology, although it is thought to be most common (almost exclusively) in tumours with adenocarcinoma histology (that is, non-squamous histology) which represent 36% of NSCLC patients (Royal College of Physicians. National Lung Cancer Audit 2016 [for the audit period of 2015]. Published January 2017) and is uncommon in tumours with squamous cell carcinoma histology. People with NSCLC who have an ALK fusion gene are mutually exclusive to epidermal growth factor receptor (EGFR) mutations, unless later mutation occurs. Accordingly, people with the ALK fusion gene do not receive drugs that inhibit EGFR tyrosine kinase, such as erlotinib, gefitinib and afatinib.	Comment noted. The background section of the scope has been updated accordingly.

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		Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2015, approximately 33,000 people were diagnosed with NSCLC in England. Approximately 5% of people with stage III or IV non-squamous (adenocarcinoma) NSCLC have ALK fusion genes, equating to around 400-500 people in England & Wales. For the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life. Treatment choices are influenced by the presence of biological markers (such as mutations in EGFR, ALK or PD-L1 status; histology (squamous or non-squamous) and previous treatment experience.	
The technology/ intervention	Takeda	Besides in the mentioned phase 2 study (ALTA) brigatinib has also been studied in a phase 1 and 2 study (Gettinger et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. The Lancet Oncology. Volume 17, No. 12, p1683-1696, December 2016). Brigatinib is administered as a single convenient daily dose which allows for non-hospital administration.	Comment noted. The technology section of the scope has been updated to mention the additional safety study.
	BTOG-NCRI-ACP-RCP	Yes; the licensed dose should be considered.	Comment noted. No action taken.
Population	Takeda	The population is defined appropriately. No groups with the population should be considered separately.	Comment noted. No action required.
	BTOG-NCRI-ACP-RCP	Yes; No additional groups should be considered separately	Comment noted. No action required.

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	Royal college of pathologists	As this is for treatment after progression on crizotinib, then the ALK +ve population is already screened for and this should not impact on RCPath members	Comment noted. No action required.
Comparators	Takeda	Yes.	Comment noted. No action required.
	BTOG-NCRI-ACP-RCP	Yes, ceritinib is the most appropriate comparator	Comment noted. No action required.
Outcomes	Takeda	Yes.	Comment noted. No action required.
	BTOG-NCRI-ACP-RCP	Yes.	Comment noted. No action required.
Economic analysis	Takeda	The economic analysis is specified appropriately. However, the draft scope states that the use of brigatinib is conditional on ALK+ status and the economic modelling should include the costs associated with diagnostic testing for ALK status in people with advanced non-small-cell lung cancer who would not otherwise have been tested, and a sensitivity analysis should be provided without the cost of the diagnostic test. Testing is necessary in order to establish the genetic status prior to first line treatment. In the ceritinib second line NICE appraisal the Appraisal Committee noted that testing would be done before starting crizotinib so the relevant population would have been tested already and therefore concluded that the costs of testing were not a consideration for the appraisal (NICE Technology appraisal guidance TA295. Ceritinib for previously treated anaplastic lymphoma kinase positive nonsmall- cell lung cancer. Published 22 June 2016.). Therefore the economic analysis should not include ALK testing costs.	Comment noted. The scope has been updated accordingly.

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	BTOG-NCRI-ACP-RCP	The cost utility of ALK testing should not be included as ALK testing is standard and was costed in the NICE STA 406 (first line crizotinib). All patients suitable for brigatinib will already have been ALK tested and received crizotinib by definition	Comment noted. The scope has been updated accordingly.
Equality and Diversity	Takeda	No equality issues.	Comment noted. No action required.
	BTOG-NCRI-ACP-RCP	No change required for his criterion	Comment noted. No action required.
Other considerations	Takeda	None.	Comment noted. No action required.
	BTOG-NCRI-ACP-RCP	Nil	Comment noted. No action required.
Innovation	Takeda	The benefits of PFS and intracranial ORR and PFS and the improved safety profile of brigatinib vs. ceritinib represent a step change in the management of ALK positive NSCLC compared to ceritinib. Brigatinib is expected to have an impact on intracranial outcomes not captured in the QALY.	Comment noted. These benefits should be incorporated in to the economic analysis of your submission. The innovative nature of brigatinib will be considered by the committee.
	BTOG-NCRI-ACP-RCP	This is an important medicine as it is likely to be considerable more effective and less toxic than ceritinib but is not first in class in this indication and hence not a ‘step change.’	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Takeda	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? No. Where do you consider brigatinib will fit into the existing NICE pathway, Lung cancer? Yes. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Phase 1/2 and phase 2 clinical data, systematic literature reviews, indirect treatment comparisons and economic evaluation. 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. No. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). The STA process is appropriate. NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. • Would it be appropriate to use the cost comparison methodology for this topic? No, especially as the comparator PAS is commercial in confidence.	Comment noted. No action required. Comment noted. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		• Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Brigatinib has improved clinical efficacy. Cost/resource use to be determined especially in light of commercial in confidence comparator PAS. • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes. • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? No.	Comment noted. No action required. Comment noted. No action required.
	BTOG-NCRI-ACP-RCP	Where do you consider brigatinib will fit into the existing NICE pathway, Lung cancer? If approved, brigatinib will be used within its license, post crizotinib as it is potentially less toxic than ceritinib and is potentially more efficacious. If NICE currently approve 1st line alecinitb (NICE ID925) then alectinib will replace 1st line crizotinib as the preferred first-line treatment for ALK+ NSCLC, and thereafter there will be little use of brigatinib as few 1st line patients will receive crizotinib. A small number of ALK+ patients will be identified as ALK+ following first line chemotherapy. For these patients, alectinib is not NICE appraised and so crizotinib would be used, and thereafter brigatinib or ceritinib.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Takeda	None.	
	BTOG-NCRI-ACP-RCP	No	Comment noted. No action required.

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

None.