National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection

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	British Thoracic Oncology Group	Yes: wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider.	Comment noted. No action required.
	AstraZeneca	Yes: wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider.	Comment noted. No action required.
Timing Issues	British Thoracic Oncology Group	Urgency is based on the clinical need of being able to offer cancer patients the treatment if reimbursed.	Comment noted. No action required.
	AstraZeneca	[redacted]	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted]	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Oncology Group	Accurate and complete background	Comment noted. No action required.
	AstraZeneca	*NICE text:* An estimated 10% to 35% of people with NSCLC have mutations to the protein epidermal growth factor receptor (EGFR).[7] *Suggestion to amend to:* In the general population, an estimated 10% of people with NSCLC in the UK have mutations to the protein epidermal growth factor receptor (EGFR) irrespective of the stage of disease. **https://www.rcplondon.ac.uk/file/17276/download**	Comment noted. Background information has been amended to indicate estimated 10-15% people with NSCLC.
The technology/ intervention	British Thoracic Oncology Group	yes	Comment noted. No action required.
	AstraZeneca	*NICE text:* Osimertinib (Tagrisso, AstraZeneca) is a selective, small molecule inhibitor that targets the sensitising and T790M mutant forms of the EGFR-TK. Sensitising EGFR mutations refer to exon 19 deletions and exon 21 L858R point mutations. Osimertinib is administered orally.	Comment noted. Minor adjustments made to the description of technology/intervention.

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		Osimertinib does not have a marketing authorisation in the UK for the adjuvant treatment of NSCLC. It is being studied in a phase III trial for the adjuvant treatment stage Ib-IIIa EGFR mutation-positive NSCLC after complete tumour resection. An adjuvant treatment is an additional cancer treatment given after an initial treatment, to lower the risk of the cancer returning. *Suggestion to amend to:* Osimertinib (Tagrisso, AstraZeneca) is a third generation tyrosine kinase inhibitor (TKI) irreversible EGFR-TKI designed to inhibit EGFR sensitising mutations (EGFRm, commonly exon 19 deletion and L858R) and inhibit the emergence of the EGFR T790M resistance mutation, while having minimal activity against wild-type EGFR. In addition, osimertinib is able to cross the blood brain barrier therefore its usage is expected to improve CNS outcomes. Inhibition of EGFRm signalling by osimertinib prevents downstream oncogenic consequences such as cell proliferation and angiogenesis. Osimertinib is administered orally. Osimertinib does not currently have a marketing authorisation in the UK for the adjuvant treatment of NSCLC. Osimertinib is in development for the treatment of patients with resected EGFR-mutated NSCLC. The Phase III clinical trial (NCT02511106; ADAURA) is a double-blind, randomised, placebo-controlled multicentre, study to assess the efficacy and safety of osimertinib (n=339) versus placebo (n=343), in patients with EGFR mutation-positive stage IB-IIIA NSCLC, following complete tumour resection with or without adjuvant chemotherapy. An adjuvant treatment is an additional	

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		cancer treatment given after an initial treatment, to lower the risk of the cancer returning and improve long-term outcomes.	
Population	British Thoracic Oncology Group	Yes: population is defined appropriately. No: there are no groups within this population that should be considered separately.	Comment noted. No action required.
	AstraZeneca	Yes: population is defined appropriately.	Comment noted. No action required.
Comparators	British Thoracic Oncology Group	Yes: these are standard treatment(s) currently used in the NHS with which the technology should be compared.	Comment noted. No action required.
	AstraZeneca	Yes	Comment noted. No action required.
Outcomes	British Thoracic Oncology Group	Yes: the outcome measures capture the most important health related benefits (and harms) of the technology.	Comment noted. No action required.
	AstraZeneca	Yes, however the following are also a key outcome of the trial: • sites and rates of recurrence (exploratory analysis)	Comment noted. This outcome has been added to the outcomes list.
Economic analysis	British Thoracic Oncology Group	No comment.	Comment noted. No action required.
	AstraZeneca	None	Comment noted. No action required.

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Equality and Diversity	British Thoracic Oncology Group	No comment.	Comment noted. No action required.
	AstraZeneca	None	Comment noted. No action required.
Other considerations	British Thoracic Oncology Group	n/a	-
	AstraZeneca	none	Comment noted. No action required.
Innovation	British Thoracic Oncology Group	This technology is a landmark change in the treatment of EGFR mutation positive patients in the adjuvant setting. It is innovative and has the potential to have a significant positive impact in the clinical outcome of this patient group. The data comes from the ADAURA phase III clinical trial in which an early analysis of the primary endpoint of disease free survival was significantly in favour of the arm that received adjuvant Osimertinib. Although the data is immature the hazard ratio for overall survival was also significantly in favour of the Osimertinib treated group.	Comment noted. No action required.
	AstraZeneca	Current guidelines state that following complete tumour resection with or without adjuvant chemotherapy, patients with EGFR positive NSCLC have no treatment alternatives other than active monitoring. Despite the early nature of the disease and complete resection of the tumour in patients with early stage NSCLC, UK data shows that recurrence rates remain high with an estimated 45% with stage IB to 76% with stage III recurrence within 5 years.[1] In addition, the 5-year survival rate after surgery	Comment noted. No action required.

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		are disappointingly low, ranging from 68% in stage IB, 53-60% in stage II, and reducing to 13-36% for stage III.[1] Therefore there remains a significant need to improve the care of patients with fully resected NSCLC by reducing the risk of recurrence and improving long term survival In July 2020, osimertinib was granted Breakthrough Therapy Designation in the USA for the adjuvant treatment of patients with stage IB–IIIA EGFRm NSCLC after complete tumour resection with curative intent, due to the unprecedented results from the ADAURA study. The interim analysis showed that at 24 months, 90% of the patients with stage II to IIIA disease in the osimertinib group (95% confidence interval [CI], 84 to 93) and 44% of those in the placebo group (95% CI, 37 to 51) were alive and disease-free (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26;P<0.001). [redacted]	

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		Osimertinib therefore offers patients with EGFRm NSCLC an innovative step change treatment option following complete resection with or without adjuvant chemotherapy and will represent the first targeted agent to improve long term outcomes for patients with fully resected early stage NSCLC. [1] Pignon et al. J Clin Oncol 2008;26:3552-3559	
Questions for consultation	British Thoracic Oncology Group	**What is the current standard care for people with NSCLC after complete tumour resection (with or without adjuvant chemotherapy)?** 4 cycles of platinum based chemotherapy **Would treatment with osimertinib be given in addition to standard care, or it would replace some elements of standard care?** In the ADAURA clinical trial standard of care (4 cycles of platinum based chemotherapy) in the experimental arm prior to receiving Osimeritnib was not mandated and left to clinician' discretion. Approximately two-thirds of patients did receive chemotherapy prior to Osimertinib. The hazard ratio was in favour for the Osimertinib arm regardless of whether chemotherapy was administered prior to Osimertinib. Based on this this I would expect Osimertinib to be given in addition to standard of care – although it is highly conceivable that if reimbursed a reasonable proportion of patients will not receive chemotherapy and will move immediately to adjuvant Osimertinib.	Thank you for your responses.

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		Have all relevant comparators for osimertinib been included in the scope? The comparator has not been formally defined, but would be 4 cycles of platinum based chemotherapy **Are the outcomes listed appropriate? Are all relevant outcomes listed?** Yes Yes **Are there any subgroups of people in whom osimertinib is expected to be more clinically effective and cost effective, or other groups that should be examined separately?** No **Where do you consider osimertinib will fit into the existing NICE pathway for Treating non-small-cell lung cancer (2020)?** In the 'chemotherapy after surgery' section **Is testing for EGFR mutations currently routinely done for early-stage NSCLC?** No – EGFR testing is not routinely performed at all centres in early-stage disease.	

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		If the treatment is reimbursed this would need to be implemented. **Do you consider osimertinib 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)?** **Do you consider that the use of osimertinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** This technology is a landmark change in the treatment of EGFR mutation positive patients in the adjuvant setting. It is innovative and has the potential to have a significant positive impact in the clinical outcome of this patient group. The data comes from the ADAURA phase III clinical trial in which an early analysis of the primary endpoint of disease free survival was significantly in favour of the arm that received adjuvant Osimertinib. Although the data is immature the hazard ratio for overall survival was also significantly in favour of the Osimertinib treated group. **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.**	

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		Although not a barrier, as stated above for the adoption of this technology, EGFR testing in early-stage disease will need to be performed routinely.	
	AstraZeneca	**Would treatment with osimertinib be given in addition to standard care, or it would replace some elements of standard care?** It is anticipated that osimertinib will be used in addition to active monitoring, following complete surgical resection with or without adjuvant chemotherapy. **Where do you consider osimertinib will fit into the existing NICE pathway for Treating non-small-cell lung cancer (2020)?** It is anticipated that osimertinib will be a treatment option for patients with EGFRm NSCLC following complete resection with or without adjuvant chemotherapy. It will offer an alternative therapy to current standard of care which is active monitoring.	Thank you for your responses. The scoping table was adjusted to reflect this information.

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		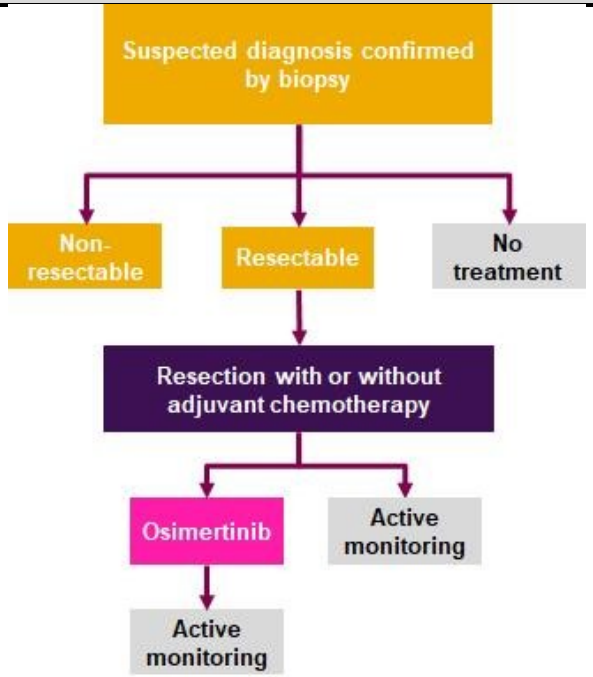 **Is testing for EGFR mutations currently routinely done for early-stage NSCLC?** Since the approval of first generation TKIs, EGFR mutation testing has become widely adopted as routine NHS clinical practice. However, testing is underutilised in early stage NSCLC because, until now, there have been no targeted therapies for these patients.	

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		Early EGFR testing is included in REFLEX testing which is recommended as routine clinical practice in clinical guidelines across the UK. Following engagement with UK clinicians, it is expected that with the introduction of a targeted therapy into UK treatment pathway such as osimertinib, there would be value in implementing EGFR/REFLEX testing in all patients irrespective of the stage of their disease. **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.** There are no anticipated barriers for adoption. As previously discussed, it is expected that the majority of patients would be subject to EGRF/REFLEX testing following the introduction of a targeted therapy for patients with earlier stages of NSCLC.	

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

- EGFR Positive UK