National Institute for Health and Care Excellence

Health Technology Evaluation

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca UK	No comments. Evaluation and proposed route are appropriate for this topic	Thank you for your comment. No action required.
Wording	AstraZeneca UK	Yes. wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology that NICE should consider	Thank you for your comment. No action required.
Timing	AstraZeneca UK	Adjuvant osimertinib remains the only treatment option available for patients with EGFRm NSCLC following complete resection with or without adjuvant chemotherapy. The ADAURA trial was the first, and	Thank you for your comment. NICE has scheduled this topic into

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		thus far, only, global trial for an EGFR-TKI inhibitor to demonstrate a statistically and clinically meaningful benefit for this population. 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.[1] Subsequently, osimertinib for this indication became the first authorisation by the MHRA under Project Oribis.[2] Since, these approvals and the original NICE appraisal (TA761), further readouts from the ADAURA trial have been published, demonstrating a consistent DFS and OS benefit with more mature data. Therefore, it is important to facilitate a timely appraisal of the technology to enable routine commissioning.	its work programme. No action required.
Additional comments on the draft remit	AstraZeneca UK	It is suggested to amend the text describing "The Technology" 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 and CNS DFS data from the ADAURA trial demonstrate clear CNS efficacy with osimertinib.[3] Inhibition of EGFRm signalling by osimertinib prevents downstream oncogenic consequences such as cell proliferation and angiogenesis. Osimertinib is administered orally. Osimertinib (Tagrisso, AstraZeneca) was granted marketing authorisation by the MHRA in May 2021 under Project Orbis for	Thank you for your comment. 'The technology' only specifies the licenced population and does not include details of the date and type of marketing authorisation for a technology. Also, the scope template no longer contains a description of the technology's mechanism of action. No action required.

Section	Stakeholder	Comments [sic]	Action
		adjuvant treatment after complete tumour resection in adult patients with stage 1b to 3a NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.[2]	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca UK	No comments	Thank you for your comment. No action required.
Population	AstraZeneca UK	Yes. The population is appropriately defined.	Thank you for your comment. No action required.
Subgroups	AstraZeneca UK	There are no subgroups within the population that should be considered separately. While the subgroup analysis of overall survival for subgroups according to stage (IB, II and IIIA) demonstrated the survival benefit was consistent across the subgroups, patients with stage IB disease comprise only 212 patients in total and only 24 OS events have occurred across both arms. The subgroups were not powered for statistical significance and therefore, are not considered sufficiently robust for decision-making. This is aligned with the approach taken in the original appraisal (TA761), which made a recommendation based on the ITT data.[4]	Thank you for your comment. The subgroups have been kept in the scope to align with that for NICE technology appraisal 761. No action required.
Comparators	AstraZeneca UK	The only relevant comparator for this appraisal is established clinical management without osimertinib (that is, active monitoring). Platinum-based chemotherapy is not an appropriate comparator. Postoperative (adjuvant) chemotherapy was allowed but was not mandatory prior to randomisation to adjuvant osimertinib or placebo in the ADAURA trial.	Thank you for your comment. To keep the scope broad, platinum-based chemotherapy

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		60% of patients in both the osimertinib and placebo arms received platinum-based adjuvant chemotherapy prior to randomisation. Therefore, adjuvant chemotherapy would not be appropriate to include as a comparator.[5] An exploratory analysis of the use of adjuvant chemotherapy and outcomes in the ADAURA trial was published in 2021. The analysis demonstrates that a consistent DFS benefit with osimertinib versus placebo was observed across disease stages IB to IIIA in ADAURA, irrespective of whether patients received adjuvant chemotherapy prior to randomisation. It was also noted that "the ADAURA trial was not designed to define the optimal role of adjuvant chemotherapy in resected EGFRm NSCLC. Patients were not randomized to compare adjuvant chemotherapy versus adjuvant osimertinib, nor were they stratified by adjuvant chemotherapy use. Hence, we cannot compare efficacy in these two groups within treatment arms".[6] Furthermore, ADAURA was not powered to assess the efficacy of osimertinib with or without adjuvant chemotherapy and chemotherapy was administered prior to randomisation. Therefore, it would be inappropriate to conduct any cost-effectiveness analyses of osimertinib with or without chemotherapy compared with adjuvant chemotherapy alone. In line with the ADAURA trial design, established UK clinical practice allows adjuvant osimertinib to be administered to patients following complete resection regardless of whether they have also received postoperative chemotherapy, and the use of postoperative chemotherapy is based on physician and patient choice.	has not been removed as a comparator.

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		The use of active monitoring as the only comparator for this appraisal is consistent with the original appraisal (TA761) and reflects the real-world use of osimertinib in UK clinical practice.[4]	
Outcomes	AstraZeneca UK	Yes. The outcomes listed are appropriate.	Thank you for your comment. No action required.
Equality	AstraZeneca UK	No equality issues have been identified	Thank you for your comment. No action required.
Other considerations	AstraZeneca UK	No additional comments.	Thank you for your comment. No action required.
Questions for consultation	AstraZeneca UK	**Where do you consider osimertinib will fit into the existing care pathway for completely resected EGFR mutation-positive non-small-cell lung cancer?** 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. This is in line with the current NICE CDF recommendation for adjuvant osimertinib (TA761).[4]	Thank you for your comment. To keep the scope broad, platinum-based chemotherapy has not been removed as a comparator.

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		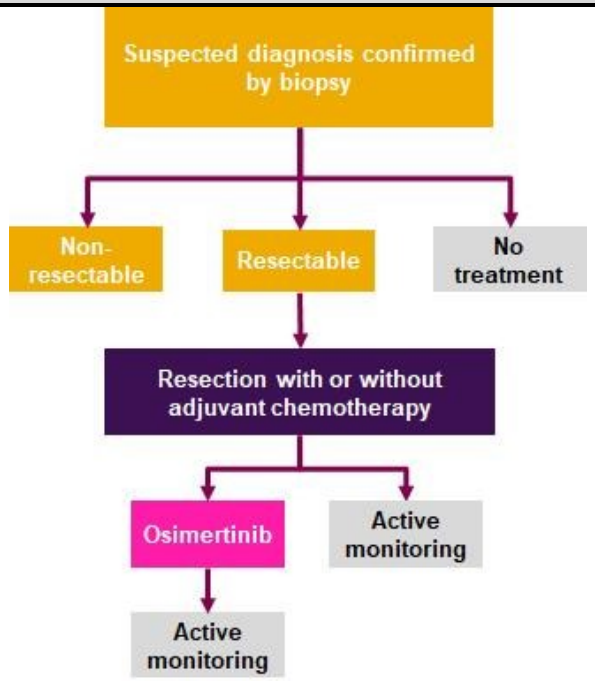 **Is adjuvant chemotherapy an appropriate comparator for osimertinib for completely resected EGFR mutation-positive non-small-cell lung cancer?** As per comments under the 'comparator' section, adjuvant chemotherapy is not an appropriate comparator for osimertinib for completely resected EGFR mutation-positive non-small-cell lung cancer.	

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		How is early-stage non-small-cell lung cancer defined in terms of cancer stages? In whom would a complete resection be offered in clinical practice? Early-stage NSCLC is defined as stage I-IIIA disease. Patients with stage I-IIIA are eligible for complete resection.[7] **Would people who had neo-adjuvant (before surgery) systemic therapy have adjuvant osimertinib in clinical practice?** The Blueteq prescribing form for adjuvant osimertinib asks for confirmation that "the patient did not receive pre-operative systemic therapy (cytotoxic chemotherapy, immunotherapy, EGFR-targeted tyrosine kinase inhibitors) for the NSCLC." This is aligned with the inclusion/exclusion criteria for the ADAURA trial. Therefore, it is not expected that people who have received neo-adjuvant systemic therapy go on to receive adjuvant osimertinib in clinical practice.	
Additional comments on the draft scope	AstraZeneca UK	No additional comments.	Thank you for your comment. No action required.

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

- EGFR Positive UK
- John Hutton – formerly of YHEC