National Institute for Health and Care Excellence

Health Technology Evaluation

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

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	No comments. The proposed route is appropriate for this topic.	Thank you for your comment.
	BTOG	This is an important topic looking at a population with potentially curative cancer, but where present outcomes are poor. A single technology appraisal is appropriate	Thank you for your comment.
Wording	AstraZeneca	The wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology that NICE should consider.	Thank you for your comment.
	BTOG	The wording seems appropriate	Thank you for your comment.
Timing issues	AstraZeneca	No timing issues identified.	Thank you for your comment.

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	BTOG	This is a relatively small population but where outcomes are poor and could be improved. Most patients will subsequently relapse and end up on Osimertinib in the metastatic setting which may be a less appropriate use of resources	Thank you for your comment.
Additional comments on the draft remit	AstraZeneca	None	N/A
	BTOG	None	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	No comments.	N/A
	BTOG	Page 1 “It is being studied in a phase 3 clinical trial “ should read it has been studied? Page “Osimertinib does have a marketing authorisation for use as an adjuvant treatment of EGFR genetic alteration positive NSCLC after complete tumour resection Should read “Osimertinib does have a marketing authorisation for use as an adjuvant treatment of NSCLC with one of the two common EGFR mutations, exon 19 deletion or L858R, after complete tumour resection:	Thank you for your comment. The LAURA trial is ongoing so the wording on page 1 has been retained. The marketing authorisation wording has been amended in line with this comment.
Population	AstraZeneca	Yes, the population is defined appropriately.	Thank you for your comment.

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	BTOG	Yes	Thank you for your comment.
Subgroups	AstraZeneca	There are no subgroups within the population that should be considered separately. There was a consistent treatment effect observed for osimertinib across the majority of subgroups in the phase III LAURA trial[1]. [1] Aredo, Jacqueline V et al. "Durvalumab for Stage III EGFR-Mutated NSCLC After Definitive Chemoradiotherapy." *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* vol. 16,6 (2021): 1030-1041. doi:10.1016/j.jtho.2021.01.162	Thank you for your comment. The subgroups have been kept inclusive at this point to allow committee to consider the cost-effectiveness estimates in any subgroups where evidence is identified.
	BTOG	Sub-groups identified are appropriate but also need to consider exon 19 deletion vs L858R	Thank you for your comment. The subgroups section has been amended to include this subgroup.
Comparators	AstraZeneca	The only relevant comparator for this appraisal is established clinical management without osimertinib (that is, best supportive care). Durvalumab is not an appropriate comparator for osimertinib for unresectable EGFR mutation-positive (EGFRm) non-small cell lung cancer (NSCLC) post-chemoradiotherapy (CRT). This is based on ESMO consensus guidelines that do not recommend the use of consolidation immune checkpoint inhibitor (ICI) therapies after curative intent CRT in EGFRm disease[2]. In addition, the impact of ICI treatment on survival outcomes for EGFRm patients is	Thank you for your comment and the links to the evidence provided. The comparators are kept inclusive at this stage to allow committee to fully consider the evidence

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		unclear[3,4]. Also, sequencing of ICI and EGFR-TKIs can result in increased risk of toxicity[5,6,7] [2] Passaro, A et al. "ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer." Annals of oncology : official journal of the European Society for Medical Oncology vol. 33,5 (2022): 466-487. doi:10.1016/j.annonc.2022.02.003 [3] Naidoo, Jarushka et al. "Brief Report: Durvalumab After Chemoradiotherapy in Unresectable Stage III EGFR-Mutant NSCLC: A Post Hoc Subgroup Analysis From PACIFIC." Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer vol. 18,5 (2023): 657-663. doi:10.1016/j.jtho.2023.02.009 [4] Girard N, Bar J, Garrido P, Garassino MC, McDonald F, Mornex F, Filippi AR, Smit HJM, Peters S, Field JK, Christoph DC, Sibille A, Fietkau R, Haakensen VD, Chouaid C, Markman B, Hiltermann TJN, Taus A, Sawyer W, Allen A, Chander P, Licour M, Solomon B. Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study. J Thorac Oncol. 2023 Feb;18(2):181-193. doi: 10.1016/j.jtho.2022.10.003. Epub 2022 Oct 25. PMID: 36307040. [5] *Schoenfeld, A J et al. "Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib." Annals of oncology : official journal of the European Society for Medical Oncology vol. 30,5 (2019): 839-844. doi:10.1093/annonc/mdz077* [6] Calles, Antonio et al. "Checkpoint Blockade in Lung Cancer With Driver Mutation: Choose the Road Wisely." American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting vol. 40 (2020): 372-384. doi:10.1200/EDBK_280795 [7]Aredo, Jacqueline V et al. "Durvalumab for Stage III EGFR-Mutated NSCLC After Definitive Chemoradiotherapy." Journal of thoracic oncology : official publication of the International [8] (Food and Drug Administration (FDA). Clinical Trial Endpoints for the Approval of Lung Cancer Drugs and Biologics Guidance for Industry. Available from: https://www.fda.gov/media/71195/download. 2018. Last accessed: August 2023	for each potential comparator. The company are advised to include justification in the submission if they choose to exclude any comparators.

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		[9] European Medicines Agency (EMA). Guideline on the evaluation of anticancer medicinal products in man. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf. Last accessed: August 2023. 2017;2020.	
	BTOG	Yes	Thank you for your comment.
Outcomes	AstraZeneca	Disease free survival (DFS) is not an appropriate outcome for this appraisal. This outcome is typically used in clinical trials of adjuvant therapies (therapies used after resection of a tumour)[8,9]. The LAURA trial studied osimertinib as a maintenance therapy in locally advanced, unresectable NSCLC and did not collect DFS. Progression-free survival was the primary outcome of this trial used to assess the efficacy of osimertinib, as maintenance therapy, compared with placebo. All other outcomes listed in the draft scope are appropriate.	Thank you for your comment. This outcome has been retained in the scope to allow discussion by committee if appropriate, and in light of other consultation comments.
	BTOG	Would also include CNS relapse as an important and common event in this populations with more impact in UK on quality of life than in most countries due to DVLA driving rules and has high associated treatment costs.	Thank you for your comment this has been included as an outcome.
Equality	AstraZeneca	No equality issues have been identified.	Thank you for your comment.
	BTOG	No major equality impact envisaged.	Thank you for your comment. This will be included in the

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		EGFR mutation cancer is found more commonly in key demographics including female gender and those ethnically from East Asia and the Indian sub-continent.	equalities impact assessment.
Other considerations	AstraZeneca	No additional comments.	N/A
	BTOG	None	N/A
Questions for consultation	AstraZeneca	**Where do you consider osimertinib will fit into the existing care pathway for NSCLC?** It is anticipated that osimertinib will be a treatment option for patients with locally advanced EGFRm NSCLC whose disease has not progressed during or following platinum-based chemotherapy **Are the comparators suggested above appropriate?** Best supportive care is the only relevant comparator. Durvalumab should not be considered for EGFRm patients, as recommended in ESMO guidelines, due to the unclear efficacy and the potential increased risk of toxicity[2-7] **What would best supportive care involve for NSCLC that is not treated with durvalumab maintenance?** Best supportive care would involve active monitoring.[1] **Are the outcomes suggested above appropriate? (Specifically, is disease-free or progression-free survival the most appropriate outcome)** Progression-free survival (PFS) is the most appropriate outcome. Disease free survival (DFS) is typically used in clinical trials of adjuvant therapies. PFS is also the primary endpoint used in the LAURA trial. In the locally advanced,	Thank you for your responses to the consultation questions, these have been considered in finalising the scope.

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		unresectable setting, patients may benefit from a longer treatment duration or a treatment to progression approach to ensure they remain progression free. **Is testing for EGFR genetic alterations routine for unresectable locally advanced NSCLC?** **At what point in the pathway is testing for EGFR genetic alterations usually carried out?** EGFR testing is included ahead of MDT and treatment decisions in the NICE Optimal lung cancer pathway and is routinely conducted in the NHS.[10] **Would a PD-L1 inhibitor be used in unresectable locally advanced NSCLC which is positive for an EGFR mutation?** The ESMO guidelines state that a PDL-1 inhibitor should not be used in the EFGRm population due to the unclear efficacy and the potential to increase the risk of toxicity[2-7]. **Would use of osimertinib as maintenance after platinum based chemoradiation affect the use of EGFR specific targeted treatments in the advanced and metastatic decision space? If so, how?** The use of osimertinib in the locally advanced unresectable setting would delay disease progression to metastatic disease and/or death. This would impact the prescribing of EGFR targeted therapies in the metastatic setting by delaying the initiation of treatment.	
	BTOG	Where do you consider osimertinib will fit into the existing care pathway for NSCLC?	Thank you for your responses to the

[10] National Institute for Health and Care Excellence. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. DG9. 2013;Available at https://www.nice.org.uk/guidance/dg9 Accessed 4th March 2024.

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		Would be integrated into the care of all unresectable stage 3 patients treated with concurrent chemo-radiotherapy with curative where a CT scan at end of treatment showed response or stable disease (about 90% of those patients) and who meet any Performance Status requirements set within funding criteria Would osimertinib be a candidate for managed access? **Yes given disease control benefits and poor outcomes observed with SoC I would be in favour of a managed or early access to medicine programme whilst license and funding were agreed.** Do you consider that the use of osimertinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Yes. I think the reduction or delay in CNS disease may give extra benefits in the UK environment given a) the present DVLA driving rules and b) discrepant standards of CNS surveillance and poor availability of MRI scanners and neuroradiology reporting.** Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **Difficult to capture. The Marsden presented their experience of SRS in the UK at ASCO 2024 https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.e14011** Are the comparators suggested above appropriate?	consultation questions, these have been considered in finalising the scope.

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		Yes What would best supportive care involve for NSCLC that is not treated with durvalumab maintenance? **Some patients may get 1-2 cycles of chemotherapy after the concurrent chemo-radiotherapy aspects of their care. Otherwise SoC would consist of surveillance for relapse. This normally consists of CT scans every 3 months approximately; however patients often need PET scans +/- biopsies to confirm recurrence as CT scans become very difficult to interpret on relapse.** Are the outcomes suggested above appropriate? (Specifically, is disease-free or progression-free survival the most appropriate outcome) **Yes. Disease Free Survival is an important outcome in this curative setting. As described above radiological relapse is often difficult to determine in this setting.** **Overall survival is the cleanest end-point but give that the vast majority of patients in the SoC arm received Osimertinib in the metastatic setting which leads to a significant survival benefit here, this may be difficult to demonstrate both in clinical trials and in a lesser extent in the real world.** **There is potentially a marked difference in both quality of life, and ability to continue to contribute to society (ie working or in a caring role) between a patient receiving Osimertinib in a maintenance "curative "setting" compared to receiving it in the metastatic setting particularly if suffering from CNS disease**.	

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		Is testing for EGFR genetic alterations routine for unresectable locally advanced NSCLC? **Yes** At what point in the pathway is testing for EGFR genetic alterations usually carried out? **As a reflex test at time of biopsy confirming non squamous lung cancer** Would a PD-L1 inhibitor be used in unresectable locally advanced NSCLC which is positive for an EGFR mutation? **At present time this is allowed within NHS funding rules, and may be used by some clinicians who are not fully aware of the emerging data and clinical opinion.** **Unplanned sub-group analysis of the PACIFIC study has suggested limited or no efficacy of durvalumab in this population which has been replicated in real world series (PMID: 36841540/ PMID: 33588109/ PMID: 38278303)** **Not only does use of durvalumab in this context lead to the potential toxicity of the immunotherapy, but it also increases the toxicity of Osimertinib if it is then used after a short time interval on metastatic relapse with a significantly higher incidence of adverse events including pneumonitis (PMID: 30847464)**	

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		Would use of osimertinib as maintenance after platinum based chemoradiation affect the use of EGFR specific targeted treatments in the advanced and metastatic decision space? If so, how? **Yes. Given that treatment is given beyond progression, in general this would suggest that on progression disease would be Osimertinib resistant. There will a sub-group who will stay on Osimertinib either because progression is limited in number of sites and amenable to local ablative therapies or more commonly as patients and clinicians are reluctant to move to chemotherapy regimens.** **If there is a systemic therapy switch (which would be recommended if the patient was fit enough) then options in the NHS would either be carboplatin and pemetrexed or carboplatin, paclitaxel, atezolizumab and bevacizumab.**	
Additional comments on the draft scope	AstraZeneca	None	N/A
	BTOG	None	N/A

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

Roy Castle Lung Cancer Foundation