Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from AstraZeneca**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. EGFR Positive

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: **5pm** on **Thursday 18 July 2024**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted] [redacted], AstraZeneca UK

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Summary	**Summary** AstraZeneca UK (AZUK) appreciate the opportunity to consult on the draft guidance for this appraisal following the Committee Meeting on the 6th of June 2024. We are disappointed that a negative draft recommendation has been issued and are concerned that the Committee preferred assumptions on long-term survival are overly conservative, lack validity and are inconsistent with the evidence base and expert opinion. We have responded to specific concerns in the sections below and have provided further scenarios and sensitivity analyses around the cure timepoints to facilitate Committee decision making. Further, we provide additional evidence on the age of diagnosis data from a large dataset of UK patients with EGFR+ NSCLC to support the generalisability of the ADUARA clinical trial to the UK setting. Whilst we acknowledge residual uncertainty in the long-term outcomes, it is important to recognise that osimertinib is a highly efficacious and well-tolerated treatment, that has been practice changing for patients in the UK during this period of managed access. The ADAURA clinical trial, which was unblinded two years early due to overwhelming efficacy, demonstrated an 73% reduction in the risk of disease recurrence or death (DFS) with use of adjuvant osimertinib in comparison with active monitoring (HR: 0.27; 95% CI 0.21, 0.34). Moreover, results of the final OS analysis underlined this efficacy with a statistically significant 51% reduction in the risk of death after a median follow-up of approximately 5-years (HR: 0.49 (95% CI 0.34, 0.70; p<0.0001)[1-6]. We remain confident that the clinically-validated approach used to inform the cure timepoint in the company submission is appropriate for decision making; however, we have amended the following assumptions in the company base case to reflect committee feedback: • Increased osimertinib retreatment rate from 50% to 60% in the advanced setting • Reduced treatment gap between completion of adjuvant osimertinib and initiation of osimertinib in the advanced setting from 12-months to 6-months Implementing these changes results in an increase in the ICER from £17,156 per QALY gained to £20,897 per QALY gained (Table 1). The predicted 11% increase in the maximum cure proportion in the company base case is likely conservative given clinical expert validation and the meaningful and statistically significant benefit observed in ADAURA. The company have provided additional scenario analyses to assess the impact of cure assumptions. Clinicians have confirmed that at least some patients should be considered cured at 5-years on treatment with osimertinib, consistent with the committee's preferred assumptions for active monitoring. Of these scenario analyses, only two fulfilled this criteria: 1) cure applied at 5-years to both osimertinib and active monitoring, and the company base case, which aims to capture the uncertainty of the cure proportion between 5 and 8 years in the osimertinib arm. These scenarios have a high likelihood of cost-effectiveness at a £20,000 - £30,000 per QALY gained threshold, with an **ICER range between £4,211 - £20,897 per QALY gained.**

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1	**The committee's preferred cure assumptions stated in the ACD are highly conservative, resulting in a 1% maximum incremental cure rate for osimertinib versus active monitoring, which is inconsistent with the evidence base and clinical expert opinion** The concept of a functional cure is well established in this disease setting and informs the clinical management of patients in practice. A 5-year timepoint is commonly used, whereby patients who remain disease-free at 5-years are considered to have a very low (non-zero) risk of recurrence. In this appraisal, the Committee accepts that this is a reasonable assumption for patients in the active monitoring arm, with a 5% residual risk of recurrence (95% considered cured) after this timepoint. In TA761 (the original appraisal of this indication)[7], the Final Appraisal Document (FAD) concluded that osimertinib was likely to result in a functional cure with a timepoint between 5 and 8 years. Although highlighted as a key area of uncertainty on entering the Cancer Drugs Fund, it was never likely to be fully resolved within this period and indeed the SACT data are too immature to be informative. Nevertheless, additional data collected from the Final OS analysis in the ADAURA trial have demonstrated sustained DFS with a statistically significant 51% reduction in OS after a median follow-up of approximately 5-years [HR: 0.49 (95% CI 0.34, 0.70; p<0.0001]. As described in the company Submission (CS), in order to inform an appropriate cure timepoint for osimertinib, extensive validation was conducted through 1:1 interviews with five clinical experts in the UK. Although clinical opinion did vary on the specific cure timepoint (between 5 and 8 years), all clinicians consistently agreed that once cure was considered possible in the active monitoring arm, then it would follow that curative potential should also be considered for some patients in the osimertinib arm. Two of the five clinicians interviewed considered the cure assumption should be applied at 5-years for osimertinib for all patients, consistent with active monitoring. The company base case therefore took an approach to reflect this feedback by applying the same starting time point for cure in both arms and increase the proportion cured at different rates to account for uncertainty in the specific timing. This was viewed as a relatively conservative assumption given a sharp increase was modelled for the active monitoring arm (95% cured at 5 years) versus a gradual increase for the osimertinib arm (95% cured at 8 years). This approach (referred to as a 'warm-up period' in the submission) and the corresponding outcomes were fully validated by clinical experts and considered to be reflective of clinical expectation in this disease area. The absolute proportion of patients assumed to be cured in this scenario is shown in Figure 1 below.

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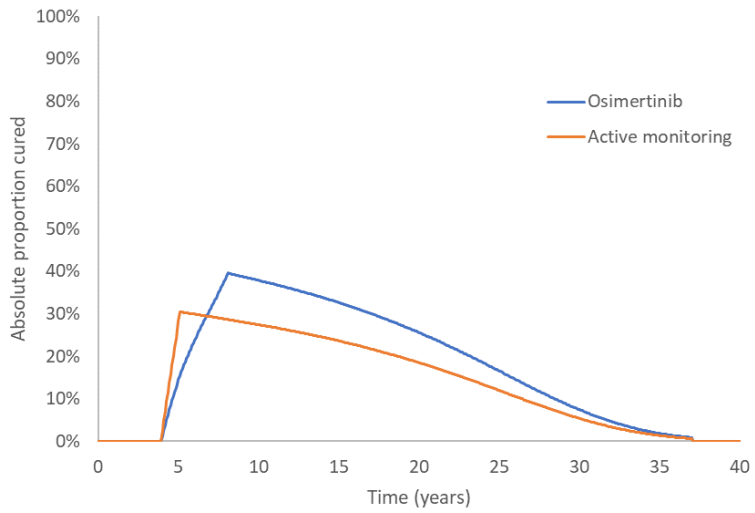
Figure 1: Company base case



As expected, the majority of patients who remain disease free are considered cured in the active monitoring arm at year 5 (95%), and a reduced gradient is observed in the osimertinib arm. In total, there is a maximum curative potential of 28% in the active monitoring arm and 39% in the osimertinib arm, resulting in an absolute difference of 11%. As stated above, this scenario draws on clinical opinion by recognising that:

- there is a common timepoint from which some patients are considered cured in both arms;
- the underlying risk of disease recurrence earlier in the follow-up period (noted as less than 36–48 months) is not representative of the risk of recurrence at later time periods, and;
- patients who are disease-free following complete tumour resection experience a far higher risk of recurrence early in the follow-up period, with the risk of recurrence decreasing over time.[8,9]

As a result, we maintain that this approach appropriately reflects the long-term curative potential of osimertinib by extending disease-free survival post-resection. External validation from clinical experts indicated that the predicted 11% increase in the curative potential was not only plausible but potentially conservative given the clinically meaningful and statistically significant DFS and OS data reported in the ADAURA study, as well as the assumption that a greater proportion of people are considered cured on active monitoring between years 4 and 7 than on osimertinib.

The committee did not agree that this approach was appropriate, despite acknowledging there was clinical support for the warm-up period. In the ACD, the warm-up period was described as 'unconventional' which does not reflect precedent established in other NICE appraisals (TA876) nor the intent to model a pragmatic approach, bespoke to this disease setting and the available data. The committee also highlighted the uncertainty associated with long-term DFS which is discussed further in response to Comment 4.

The committee instead preferred a scenario that linked the long-term survival to time on treatment, citing that the scenario generates more plausible DFS outcomes. We strongly disagree that this scenario results in a plausible interpretation of the evidence base and indeed introduces logical

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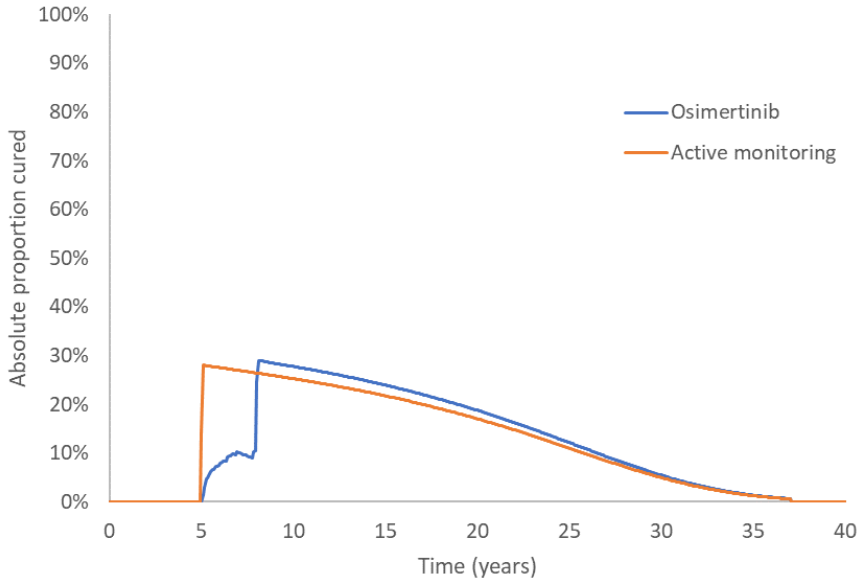
inconsistencies which lack validity. The absolute proportion of patients assumed to be cured in this scenario is shown in Figure 2 below.

Figure 2: Committee preferred base case



The interpretation of this scenario presents a number of challenges:

- The estimated maximum curative potential of 28% in the active monitoring arm and 29% in the osimertinib arm (delta 1%) is inconsistent with clinical expectation discussed above and the significant benefit in DFS and OS endpoints reported in ADAURA
- Although it appears to adopt a similar approach to the company 'warm up period', it is applied in an illogical manner, with the absolute proportion cured in the osimertinib increasing until approximately 7.5 years, then decreasing, before sharply increasing at year 8
- It explicitly assumes that discontinuation of treatment is positively correlated with earlier curative potential, which holds no biological rationale

A summary of both approaches, including cost-effectiveness results are included in Table 1 below. The assumptions included in all scenarios include retreatment permitted in the osimertinib arm after 6-months, 60% osimertinib retreatment assumed and a starting age of 63 years per the ADAURA study.

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Table 1: Company base case and committee-preferred analyses

Scenario	**Max. cure** Active Monitoring	**Max. cure** Osimertinib	**Max. cure delta**	**ICER**
Company Base Case (revised)	28%	39%	11%	£20,897
Committee preferred	28%	29%	1%	£42,344

Based on the above, and our responses to the DFS assumptions outlined in Comment 4, we believe the company Base Case scenario on cure timepoint remains the most appropriate to inform decision making and highlights that osimertinib is highly likely to continue to be a cost-effective use of NHS resources.

Nevertheless, we have also conducted a range of scenario analyses to further explore the impact of the osimertinib cure timepoint on the cost-effectiveness results (Table 2). For all scenarios, the cure assumption for active monitoring remains at 5 years and the warm-up period for both active monitoring and osimertinib has been removed. All other assumptions are consistent with the company revised base case outlined above.

Table 2: Scenario analyses

Osimertinib cure scenario	**Max. cure** Active Monitoring	**Max. cure** Osimertinib	**Max. cure delta**	**ICER**
Cure timepoint: 5 years	28%	50%	22%	£4,211
Cure timepoint: 6 years	28%	40%	12%	£14,202
Cure timepoint: 7 years	28%	32%	4%	£32,647
Cure timepoint: 8 years	28%	26%	-2%	£56,085

In summary, we consider that the company base case approach appropriately reflects the long-term curative potential of osimertinib by extending disease-free survival post-resection, and that the predicted 11% increase in the curative potential is likely conservative given the clinically meaningful and statistically significant benefit observed in ADAURA and compared with the scenarios presented in Table 2. Clinicians have confirmed that at least some patients should be considered cured at 5-years on treatment with osimertinib, consistent with the committee's preferred assumptions for active monitoring. The company base case and the scenario with cure modelled from 5 years in Table 2 are the only scenarios to appropriately capture cure from 5-years on osimertinib treatment; therefore, the **most plausible ICER range is between £4,211 - £20,897 per QALY gained.**

2

The ACD states retreatment with osimertinib occurs from 3 years after treatment initiation; however, retreatment with osimertinib in the first-line metastatic setting immediately after completing 3-years of adjuvant osimertinib treatment is clinically implausible. The assumption of a 70% retreatment rate is not supported by evidence

<u>Retreatment timepoint</u>

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	The company acknowledges that there is a lack of clinical data and experience in retreating patients in this setting. However, the committee's preferred assumptions result in a scenario that is clinically implausible, as patients are able to complete 3-years of treatment in the adjuvant setting, immediately receive a scan and diagnosis of advanced disease and start retreatment with osimertinib without delay. The company base case assumption on the retreatment period was based on interviews with clinical experts, the majority of whom agreed that they would leave at least a 12-month gap before retreatment. This is consistent with the preferred assumptions of the committee in the TA761 appraisal.[7] However, the minimum window of time stated in the clinical interviews was a 6-month treatment break. The company have updated the analysis to include this 6-month minimum treatment break with the ICER increasing from £17,156 per QALY gained to £18,409 per QALY gained versus the previous assumption. This assumption is viewed as highly conservative. This 6-month treatment gap assumption has been included in the ICERs reported in Comment 1. <u>Proportion (re)treated</u> The committee concluded that it is likely that much more than 50% of people would have osimertinib as a retreatment in the metastatic setting and assumed 70% in the base case. The evidence supporting this assumption is not reported by the committee and, in clinical practice, retreatment rates are low as osimertinib has been in the Cancer Drugs Fund for less than 3 years, with the majority of patients yet to complete 3 years of adjuvant osimertinib. Furthermore, despite the EAG clinical advisors also stating that a higher proportion of patients would be treated with first-line osimertinib in the distant metastatic recurrence setting in the active monitoring arm compared to the company base case (83%), this proportion was not increased in the committee's preferred assumptions and is potentially inconsistent with the high rate of assumed re-treatment by the committee. Recognising that there is uncertainty in this parameter, the company base case has been updated with a midpoint between the company and the committee's osimertinib retreatment assumption in the ICERs reported in comment 1. The ICER increases from £17,156 per QALY gained to £19,369 per QALY gained when applying a 60% retreatment assumption (midpoint between 50% and 70%) versus the previous company assumption of 50% retreatment with osimertinib.
3	**The committee applied the median age from the SACT dataset; however, the data are from a small sample size and inconsistent with the age of diagnosis in ADAURA and an EGFR-positive UK survey data, which show the median age of diagnosis is between 60-64 years old** The Systematic Anti-Cancer Therapy (SACT) dataset collected data on 143 patients who received adjuvant osimertinib in England during the CDF period, but the data are considered too immature and based on a small sample size (N= 143, 80% of which are still receiving treatment at the time of DCO), meaning that the SACT data should not be the primary evidence base for decision making at this stage. This includes the use of age, which the committee have stated SACT as their preferred assumption for the starting age in the economic model. The company consider adopting the baseline age from the SACT data is inappropriate and inconsistent with the age of diagnosis in the ADAURA study (63 years old), the primary evidence base for this appraisal. Baseline characteristics used in the economic model must ensure consistency with the most relevant source of evidence, i.e., the ADAURA trial, on which other key parameters are based (e.g., DFS data, treatment duration and utilities) and adopting external sources will lead to internal inconsistency in the economic analysis and bias interpretation of the

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	outcomes. Clinicians have indicated that they view the baseline characteristics of the ADAURA trial to be broadly representative of clinical practice. Furthermore, EGFR+ UK conducted a 2024 survey of 233 UK patients to understand the patient experience[10]. The EGFR+ members reported a median age of diagnosis between 60-64 years old in the survey. The age range of diagnosis, from a larger UK dataset than the SACT dataset, confirms the ADAURA study mean age of diagnosis (63 years) is appropriate for decision making.
4	**The ACD states that there remains uncertainty in the long-term DFS and OS; however, a statistically significant DFS and OS benefit has already been demonstrated for osimertinib in the ADAURA study and it is expected to result in a DFS plateau for osimertinib** The ACD comments that long-term effectiveness was a key uncertainty in the original appraisal and the EAG noted that there remains uncertainty in long-term DFS and OS, driven by the low number of events in the osimertinib arm. The ACD concludes that it is "possible that the gap between the osimertinib and placebo DFS curves will decrease over time" but ignores that the gap between the osimertinib and placebo DFS curves could also be maintained or increase over time, which is expected given that patients who remain disease-free for a sustained period (>36-48 months) have a substantially decreased risk of relapse and increased chance of cure.[8,9] The EAG advised that it was possible that a plateau could emerge for osimertinib, however this consideration was omitted from the committee's considerations regarding the cure assumptions (see Comment 2). Clinical advisors have also said that they believe the osimertinib curves would plateau with further follow-up, and that it is not plausible for a plateau to materialise for the placebo arm and not the osimertinib arm. In the plot of the within-trial DFS hazards presented during the committee meeting, it was noted that for the placebo arm, the risk of relapse or death decreased over time, whereas in the osimertinib arm the hazards increased over time with no plateau observed in the within-trial period. Towards the end of the follow-up period, there are low numbers at risk in the osimertinib arm of the ADAURA trial due to high levels of censoring at later timepoints (E.g., from year 4 to year 5 the number at risk in the osimertinib arm drops from 133 to 39); therefore, caution should be applied against adjusting the cure assumptions to fit the downward trend observed in the latter part of the DFS KM curve. In summary, the challenge of limited follow-up in order to accurately model long-term outcomes is expected in an early disease setting such as adjuvant EGFR-mutated NSCLC. Despite these challenges, osimertinib has already demonstrated a statistically significant and clinically meaningful benefit across both DFS and OS endpoints. This significant and clinically meaningful DFS and OS benefit is expected to translate to a DFS plateau, as noted by clinicians and suggested by the EAG, and an overall increase in patients cured versus active monitoring.
5	**EGFR testing is not attributable to osimertinib treatment and next generation sequencing panel tests are routine practice for patients at diagnosis, irrespective of treatment administered** EGFR mutation testing is conducted routinely in UK clinical practice for patients with NSCLC.[13,14] Clinicians interviewed in 2023 confirmed EGFR testing for early-stage NSCLC is part of routine practice and is conducted on biopsied tissue prior to surgery where possible.[15] In summary, these testing costs are not attributable to Osimertinib and should not be considered in the economic analyses.

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6	**The ACD contains some misrepresentation of the EAG report, clinical opinion, previous appraisal outcomes, and additional factual inaccuracies** There are several instances where the ACD has misrepresented the EAG report, clinical opinion or previous appraisal outcomes, as outlined below: - "In the absence of an alternative model structure, the EAG base case was the same as the company's, but with no warm-up period." This is incorrect as the EAG presented two base cases – a preferred optimistic base case (with the warm-up period) and a preferred pessimistic base case (without the warm-up period). They did not state a preference for one base case in their reporting or at the committee meeting, and both scenarios should be considered the EAG's base case analyses. - "The company advised that the difference in these final cure points was to account for the additional 3 years during which the person would have osimertinib. This was also the preferred assumption of the committee in the original appraisal." This is incorrect as the committee in the original TA761 appraisal stated they considered several modelling assumptions plausible, including cure at 5 years in both arms in the model. A scenario modelling cure at 5 years in both arms has been conducted and provided in the Comment 1 in this document (Scenario 5) to support with decision making. - "One clinical expert advised that a warm-up period should be included." This is an expert consulted by the EAG. Five clinical experts were also consulted by the company as reported in the CS and who consistently agreed that a warm-up period should be included. This statement is therefore not a complete representation of the strength of clinical opinion regarding the warm-up period. The clinical validation of the warm-up period supports it as a clinically plausible approach to modelling cure in this setting. - "It agreed that a sharp drop in risk had been seen in the DFS curves for previous tyrosine kinase inhibitors [TKI] and had concerns with applying a warm-up period to the modelling." This text does not recognise that osimertinib is a third generation TKI, which is distinctly different from second generation TKIs upon which this statement is based. Osimertinib is statistically significantly more efficacious than second generation TKIs, as evidenced in head-to-head trials, and developed to overcome known TKI resistance mechanisms[11,12]. Osimertinib has demonstrated a statistically significant and sustained DFS and OS benefit in this setting, whereas second-generation TKIs have not. It is inappropriate to utilise studies on second generation TKIs to make inferences about the survival benefit of osimertinib.

Insert extra rows as needed

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Consultation on the draft guidance document – deadline for comments: **5pm** on **Thursday 18 July 2024**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	EGFR+ UK

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] ([redacted])

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Firstly, I want to stress how disappointed EGFR+ UK is at this decision. While we accept there is some uncertainty in the calculations around cure rates, the fact that there is already evidence of a statistically significant improvement in the survival rates for those in

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	the treatment group should speak for itself. We take the position that, from a patient perspective, a 10% increase in 5-year survival rates is both clinically and personally meaningful, as is the very significant increase seen in the DFS data.
2	We have some concerns about the SACT data set which seems to be older than our membership. EGFR+ UK has over 700 members, and in a recent survey (n=233) we found the median age band to be 60-64 years. This is more in line with the ADAURA trial, than the SACT data. This may have implications in terms of the soundness of the recommendations made.
3	The uncertainty in the meeting itself was very apparent. However, as a Professor of Psychology and someone who specialises in and teaches research methods – it was also apparent that the models used by the committee were likely to inaccurate and implausible. I appreciate this may not be easily resolved, but I would urge to you to work closely with AZ to establish a model which is better able to model real life observations.
4	As I wrote in my original statement, there is a significant impact of existing treatment pathways on patient wellbeing, which adjuvant Osimertinib is likely to ameliorate. While the report acknowledges that anxiety that is associated with existing treatment pathways (i.e. adjuvant chemo or doing nothing after surgery), I can't see anywhere that takes into account the costs associated with supporting patients with clinically significant anxiety and/or depression – many of whom are likely to seek/receive psychological support from the NHS, whether pharmacological or non-pharmacological treatments (such as counselling), or complementary treatments. These costs are likely to be significantly reduced as a result of receiving adjuvant Osimertinib, and really should be included.
5	We would also contest the argument that testing for EGFR mutations should be included in the economic model. In our experience, many people with Stage 1 disease receive testing as part of their standard care. Indeed, in a recent survey 11% of our members (n=234) were diagnosed with Stage 1 disease (and 21% were diagnosed at Stages 1 or 2, which maps on to UK statistics) – all were identified as EGFR+ by genetic testing as part of their care.
6	One factor we were asked to consider was that of discrimination. I suppose the only discrimination that is apparent here is that inherent in the UK health care system as a whole. That is, those who can afford to self-fund, or who have private health care will be able to access this treatment… while those who do not, cannot. But I appreciate this is not something that can be fixed here!
7	Finally, I was disappointed with how little the patient perspective seems to have been taken into account in this appraisal. I am not sure if this is usual, but I felt as if there were not many opportunities to have the patient voice heard, and do not understand why the summary of the patient comments needs to be pared down to a single slide and presented by someone who is not a patient. I am sorry to say that it felt more like a tick box exercise than genuine patient involvement – and I had hoped more emphasis would be placed on quality of life (both from a qualitative perspective, but also in terms of the costs associated with this – see Point 4 above). I was also disheartened by the process

NICE National Institute for Health and Care Excellence

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	on the day, as it felt like a foregone conclusion. In particular, one of the people in my breakout room made it clear that they knew "which way it was going to go" before the meeting even started – which seems deeply problematic. I do hope to be involved in more of these in the future, as I am passionate about PPI and think that it is incredible important – however, I do think there is room for improvement in terms of collaboration.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Society of Cardiothoracic Surgeons UK & Ireland
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

The SCTS would ask NICE to reconsider their opinion on access to adjuvant Osimertinib which is the currently the only option for patients with EGFR positive disease after surgery. The results of the ADAURA trial underscore Osimertinib as the current most efficacious treatment with an impressive 80% reduction in the risk of death or recurrence after lung cancer surgery. The models presented by NICE are based on scenarios extrapolated far beyond (5 to 8 years and further) the approximate median follow up of approximately 2 years were punitive with uncertainties openly acknowledged by the NICE committee (section 3.2 of MA review of TA761).

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Addendum: EAG critique of the company's response to the draft guidance

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, University of Sheffield, Sheffield, UK Mon Mon Yee, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Sarah Ren, Research Associate, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, University of Sheffield, Sheffield, UK
Date completed	2nd August 2024

1. Introduction

In June 2024, the National Institute for Health and Care Excellence (NICE) published a negative recommendation for osimertinib for the adjuvant treatment of stage 1b to 3a non-small-cell lung cancer (NSCLC) after complete tumour resection in adults whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.[1] The Draft Guidance (DG) highlights uncertainty around long-term disease-free survival (DFS) and overall survival (OS) outcomes, including the cure assumptions applied in the adjuvant osimertinib group of the company's economic model. Owing to the uncertainty around long-term DFS and OS benefits, the DG comments that it is uncertain whether adjuvant osimertinib is a cure or whether it just delays the cancer coming back in the long term. The Appraisal Committee agreed that an acceptable incremental cost-effectiveness ratio war(ICER) for osimertinib versus active monitoring (AM) should be around £20,000 per QALY gained. The DG states that because of the uncertainty in the long-term clinical effectiveness, the most likely cost-effectiveness estimates are above the range that NICE usually considers an acceptable use of NHS resources.

Section 3.21 of the DG[1] details the Appraisal Committee's preferred model assumptions:

1. Using the EAG's corrections for model and costing errors (including EGFR testing costs)
2. No warm-up period prior to cure
3. Cure-point of 5 years for AM
4. Cure-point of 5 years plus time on treatment (1 minus time to treatment discontinuation [TTD] function) for adjuvant osimertinib
5. Retreatment allowed from 3 years after starting adjuvant osimertinib
6. 70% of people in the adjuvant osimertinib group who develop distant metastases will have osimertinib in the first-line setting
7. Starting age of 70 years in the economic model.

The Appraisal Committee's preferred cure assumptions are consistent with the EAG's Additional Sensitivity Analysis (ASA) 1b. The ICER for this scenario was estimated to be £37,387 per QALY gained (see EAG report,[2] Table 56). The inclusion of higher retreatment rates, an earlier retreatment timepoint, EGFR mutation testing costs and an initial patient age of 70 years also increase the ICER.

In July 2024, the company submitted a response to the NICE DG.[3] The company's response consists of a written document and an updated version of the economic model. The company's written document explains that the company disagrees with the Appraisal Committee's preferred analysis and provides a new company base case which assumes that a different proportion of people are retreated with osimertinib in the first-line metastatic setting (increasing the osimertinib retreatment rate from 50% to 60%) and applies a different time point for the initiation of osimertinib retreatment in the metastatic

setting (reducing the minimum treatment gap after discontinuing adjuvant osimertinib from 12 months to 6 months). The company's new base case analysis retains the cure assumptions applied in the company's original model (including a warm-up period starting at 4 years in both groups) and applies an initial start age of 63 years based on ADAURA.[4] The differences between the company's updated base case model and the Appraisal Committee's preferred assumptions are summarised in Table 1. The company has not amended its Patient Access Scheme (PAS) discount, which remains at [redacted].

Table 1: Summary of the Appraisal Committee's preferred analysis and the company's new base case model assumptions

Aspect of model	Appraisal Committee's preferred analysis	Company's new base case analysis	Is the new model in line with the Appraisal Committee's preferred analysis?
EAG corrections and EGFR testing costs	EGFR test costs included. Corrections included.	EGFR tests are excluded. Corrections included.	Partly
Cure assumptions (including warm-up period) and long-term DFS and OS*	No warm-up period prior to cure†	Warm-up period included (4 years for osimertinib and 1 year for AM).	No
	5 years for AM	5 years for AM	Yes
	5 years after discontinuing treatment (1 minus TTD function) for osimertinib	8 years for osimertinib	No
Osimertinib retreatment in the first-line metastatic setting	Retreatment allowed from 3 years after starting osimertinib	Retreatment allowed from 3.5 years after starting osimertinib	No
	70% retreated	60% retreated	No
Starting age in the model	70 years	63 years	No

DFS - disease-free survival; OS - overall survival; EGFR - epidermal growth factor receptor; AM - active monitoring; DM - distant metastases; TTD - time to treatment discontinuation

**The company's warm-up assumptions are applied as cycle-specific multipliers which increase approximately linearly from 0% to 95% by the final cure timepoint. These are applied in the model as a percentage reduction in the predicted probability of experiencing loco-regional or distant recurrence estimated from parametric survival models fitted to time-to-event data for these events*

†*The EAG notes that the Appraisal Committee's preferred assumptions (1-TTD + 5 years) are applied in a similar way to the company's warm-up assumptions.*

This addendum provides a summary and critique of the company's response to the NICE DG.[3] Section 2 summarises the results of the company's new base case analysis and the additional scenario analyses presented in the company's DG response. Section 3 provides a summary of the issues raised in the company's DG response together with a brief critique by the EAG. Section 4 presents additional analyses undertaken by the EAG which demonstrate the impact of reintroducing each of the Appraisal Committee's preferred assumptions into the company's new base case model.

2. Summary of results of company's new base case analysis and additional scenario analyses

Table 2 summaries the results of the Appraisal Committee's preferred analysis, the company's new base case analysis and the company's additional scenario analyses presented in the company's DG response.[3] All of the company's new analyses assume a retreatment rate of 60%, a retreatment time point of 3.5 years and a model start age of 63 years. The company's new deterministic base case ICER is estimated to be £20,897 per QALY gained.

Whilst undertaking the Appraisal Committee's preferred analysis, the EAG identified an error in the formulae used to estimate general population mortality rates conditional on age in the EAG's amended version of the model. This error only affects the Appraisal Committee's preferred scenario in which a start age of 70 years is applied. This error does not have any impact on the company's new base case or scenario analyses, or the analyses presented in the EAG report.[2] The ICER for the Appraisal Committee's preferred analysis, including the correction of this error, is estimated to be £57,450 per QALY gained.

Table 2: Results for the Appraisal Committee's preferred analysis and the company's new base case analysis and additional scenario analyses, includes PAS discount for osimertinib

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Appraisal Committee's preferred analysis (deterministic)†							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£57,450**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's new post-DG base case (deterministic)							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,897**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 1: Cure time point for osimertinib = 5 years, cure time point for AM = 5 years, no warm-up period							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£4,211**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 2: Cure time point for osimertinib = 6 years, cure time point for AM = 5 years, no warm-up period							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,202**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 3: Cure time point for osimertinib = 7 years, cure time point for AM = 5 years, no warm-up period							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,647**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 4: Cure time point for osimertinib = 8 years, cure time point for AM = 5 years, no warm-up period							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£56,085**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-

QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; DG - draft guidance; AM - active monitoring

**Undiscounted*

†Results include correction of the EAG's error.

3. Summary and critique of the company's DG response

The company's DG response[3] includes discussion around four main issues: (1) uncertainty around the proportion of patients who will achieve long-term cure following treatment with adjuvant osimertinib; (2) uncertainty around the proportion of patients who would be retreated with osimertinib following distant relapse and the time point from which retreatment may occur; (3) the age of the target population for adjuvant osimertinib and (4) the inclusion of EGFR testing costs in the economic model. The EAG notes that the analyses presented in the company's DG response include alternative scenarios for the first two of these issues only. The company also raises four points of misrepresentation and/or factual inaccuracies in the NICE DG.[1] The key points raised in the company's DG response are summarised and critiqued below.

3.1 Uncertainty around cure assumptions (Company's DG response, Issues 1 and 4)

The company's DG response[3] highlights that adjuvant osimertinib is a highly effective treatment, and refers to the results of the ADAURA trial[4] which demonstrated statistically significant benefits for osimertinib on both DFS (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.21 to 0.34; p=not reported) and OS (HR 0.49, 95% CI 0.34 to 0.70; $p<0.0001$).

The company's DG response acknowledges that there is uncertainty around long-term outcomes because no further data on recurrence are being collected following the early unblinding of ADAURA and because data collection in SACT[5] was limited, but argues that the cure assumptions in the company's original and new base case models (both of which include a warm-up period) are plausible and potentially conservative. The company's DG response states that their base case model predicts an 11% increase in the maximum proportion of patients cured with adjuvant osimertinib compared with AM, based on further analyses undertaken using the company's new base case model (shown in Figure 1 of the company's DG response). This plot is not reproduced here because the EAG believes that it is mathematically incorrect and misleading.

The company's DG response also states that the cure assumptions applied in the company's base case analysis were informed by one-to-one interviews with five clinical experts.[6] The company's response highlights opinion from the clinical experts that once cure is possible for AM, this should also be possible for patients receiving osimertinib (i.e., after 5 years). The response also states that two of the five clinicians interviewed believed that cure should be assumed at 5-years for all osimertinib-treated patients (although the EAG notes that this suggests that the remaining three experts consulted by the company did not share this view).

In addition, the company's response refers to the previous appraisal of nivolumab with chemotherapy for the neoadjuvant treatment of resectable NSCLC (TA876) as a precedent for the cure assumptions

applied in the adjuvant osimertinib model.[7] Within this previous appraisal, the company's model included a warm-up period for cure, starting at 0% in year 5 and increasing to 95% by year 7. The same cure assumptions were applied in all treatment groups in the model used to inform TA876.

The company's DG response includes two plots which purport to show the model-predicted absolute proportion of patients who are cured in the economic model: Figure 1 of the company's DG response relates to the company's base case analysis and Figure 2 shows the equivalent plot for the Appraisal Committee's preferred assumption whereby the cure proportion multipliers for osimertinib are based on one minus the TTD function plus 5 years. The plots appear to indicate that under the company's base case assumptions, the maximum increase in the proportion of patients who are cured is 11% for adjuvant osimertinib versus AM, but this difference is reduced to only 1% under the Appraisal Committee's preferred assumptions. The company argues that the low proportion of cured patients under the Appraisal Committee's preferred scenario is not a plausible interpretation of the evidence base. The company also argues that the absolute cured proportion under the Appraisal Committee's preferred cure assumptions is illogical because the function increases initially, then decreases at around 7.5 years, then increases again at around 8 years.

The company further argues that caution should be applied when adjusting the cure assumptions to fit the observed DFS data from ADAURA due to reportedly high levels of censoring in the osimertinib group after year 4 of the trial.

The company argues that the most plausible ICER range for adjuvant osimertinib is between £4,211 per QALY gained (company's scenario analysis 1, 5-year cure point in both groups) and £20,897 per QALY gained (company's new base case model), because only these scenarios include the possibility of cure at the same time point in both treatment groups.

EAG critique

The company's DG response[3] does not provide any new evidence on long-term DFS or OS outcomes for patients treated with adjuvant osimertinib. Additional analyses are presented using the company's new base case model (including the company's original cure assumptions), the Appraisal Committee's preferred cure assumptions (cure proportion in the osimertinib group = 1-TTD + 5 years), and three alternative scenarios in which a cure time point for osimertinib of 5, 6, 7 or 8 years is assumed, excluding the warm-up period (see Table 2).

The EAG's views regarding the uncertainty around long-term outcomes for patients treated with adjuvant osimertinib remain unchanged. The EAG remains concerned that the cure assumptions applied

in the company's base case analysis result in model-predicted DFS hazards which deviate from the DFS hazard that has been observed in the osimertinib group of the ADAURA trial[4] (see Figure 1 and

Figure ***2***, which have been reproduced from the EAG report[2]). As noted in Section 5.3.6 of the EAG report, one of the EAG's clinical advisors considered the company's DFS and OS projections to be clinically plausible, but commented that long-term outcomes following 3-year discontinuation of treatment were highly uncertain. The second clinical advisor was unsure whether the gaps in DFS and OS predicted by the company's model would be sustained in the longer-term. They stated that it was plausible that there may be a sustained gap which is smaller than that predicted by the company's model. The EAG's preferred optimistic and pessimistic scenarios were designed to demonstrate the impact of this uncertainty on the cost-effectiveness of adjuvant osimertinib. However, without further data collection on recurrence from ADAURA, the EAG does not believe that this uncertainty can be resolved.

Figure 1: Smoothed and empirical hazards for DFS in ADAURA, adjuvant osimertinib and active monitoring groups (reproduced from EAG report, Figure 41)

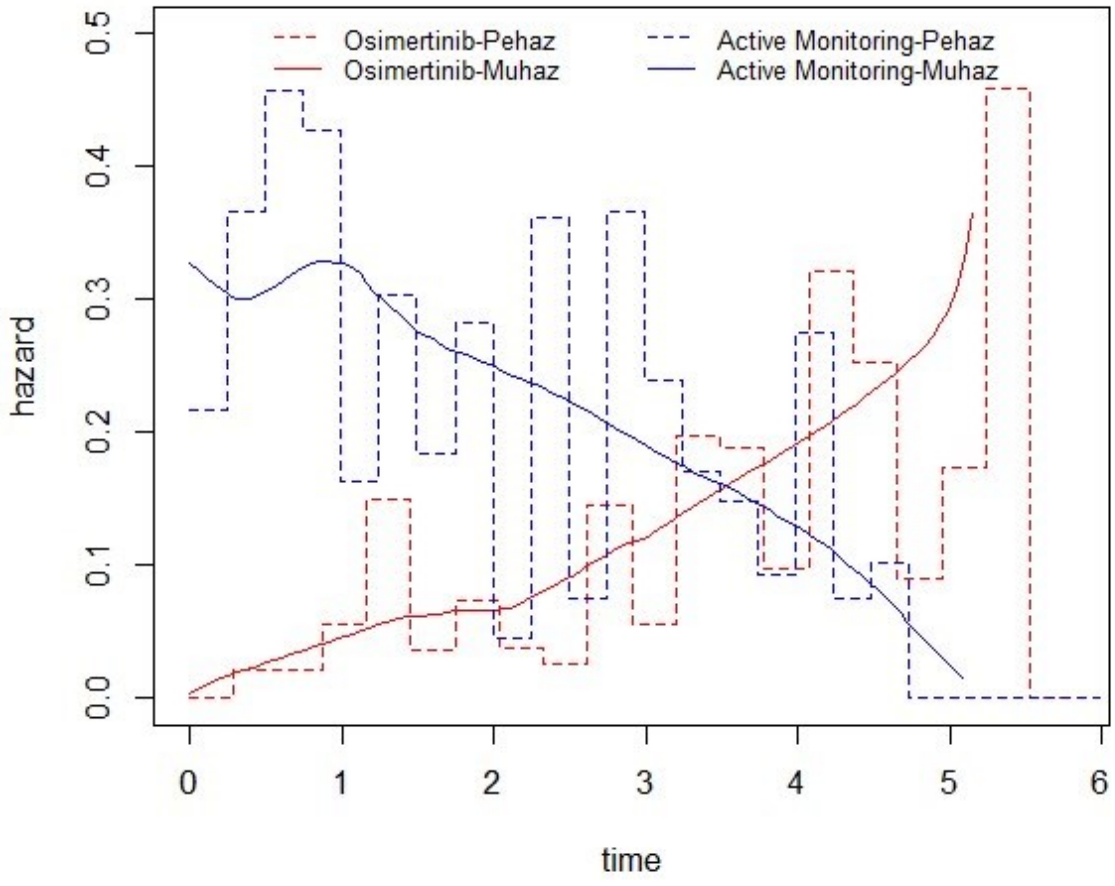
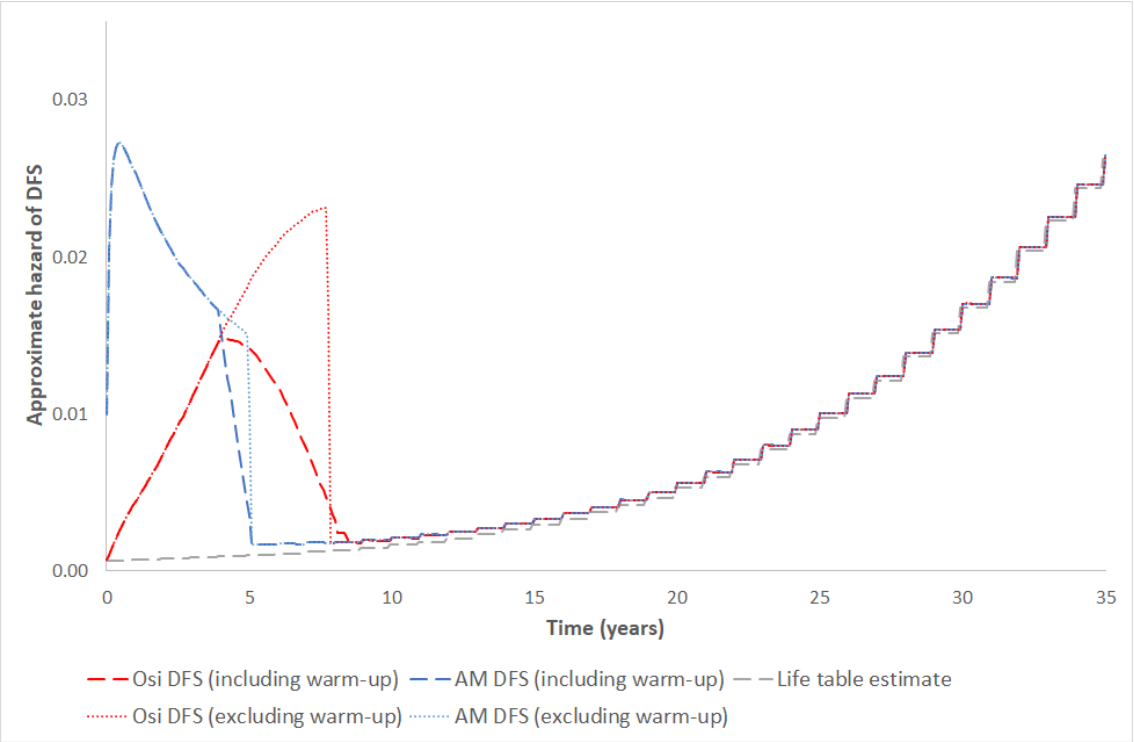


Figure 2: Company's model-predicted DFS hazards (reproduced from EAG report, Figure 43)

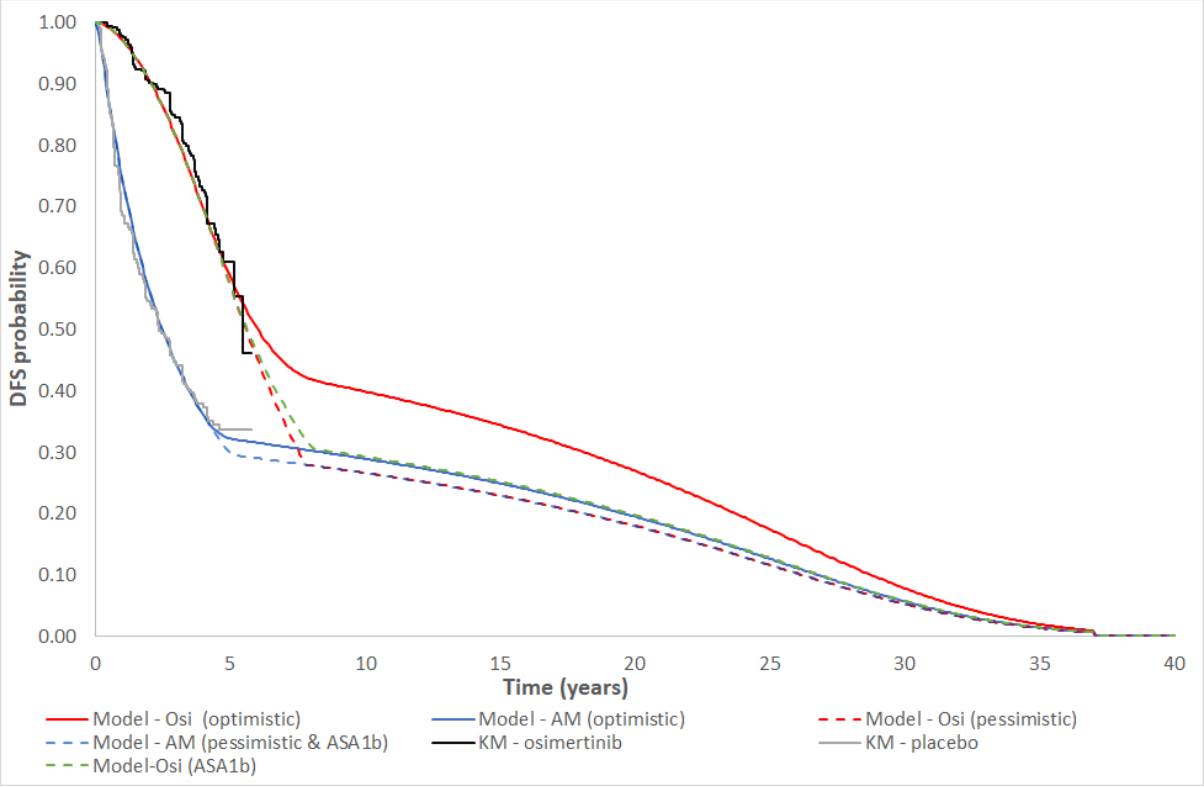


Osi - osimertinib; AM - active monitoring; DFS - disease-free survival
Notes: The company's economic model applies a cure assumption to patients receiving active monitoring starting at 0% at the end of year 4, increasing almost linearly to 95% by the end of year 5. The company's model applies a cure assumption to patients receiving adjuvant osimertinib starting at 0% at the end of year 4, increasing almost linearly to 95% by the end of year 8.

The EAG believes that the plots of the absolute cured proportion shown in Figures 1 and 2 of the company's DG response have been generated with the intention of showing that the Appraisal Committee's preferred cure assumptions are implausibly pessimistic and illogical due to their apparently anomalous pattern. The EAG believes that these plots have been calculated by multiplying the "cure proportion" values in each model cycle by the modelled DFS function. The EAG believes that this approach is mathematically incorrect and that the estimates of absolute proportions of patients cured are not interpretable. The cure proportion values used in the company's economic model are cycle-specific multipliers which are used to down-weight the predicted risk of recurrence in each cycle obtained from the fitted parametric survival models (for example, if the predicted risk of relapse in a given cycle was 5% and the cure proportion was 90%, the adjusted risk would be reduced to 0.5%). It is not appropriate to apply these cycle-specific cure proportions to the cumulative survival probabilities from the DFS function because the latter reflect the remaining population of patients who have not yet relapsed at time *t*. The company's model is structurally unable to isolate the subgroup of patients who are cured at any time point. The EAG notes however that given that patients who remain disease-free are assumed to have no excess risk of death unless they later experience distant relapse, the best way of understanding how many people have avoided relapse would be to read off the cumulative survival probabilities from the final DFS function estimated within the model trace. The impacts of the EAG's

optimistic and pessimistic cure assumptions on model-predicted DFS, as well as the Appraisal Committee's preferred scenario, are shown in Figure 3. As shown in the plot, the EAG's optimistic scenario, which retains the company's cure assumptions, predicts a substantial and sustained gap in DFS between the adjuvant osimertinib and AM groups (solid red line versus solid blue line). The Appraisal Committee's preferred cure assumptions lead to a markedly smaller gap in DFS between the groups over the model time horizon (dashed green line versus dashed blue line). The EAG's pessimistic scenario reflects a situation whereby the DFS functions meet with no subsequent gap (dashed red line versus dashed blue line).

Figure 3: Model-predicted DFS – EAG optimistic scenario, EAG pessimistic scenario and Appraisal Committee-preferred scenario (starting age = 63 years)



Osi - osimertinib; AM - active monitoring; KM - Kaplan-Meier

The company's DG response argues that the ICER range for osimertinib should be based on an assumption that the time point from which cure is possible is the same in both treatment groups. The EAG notes that this assumption is also applied in the Appraisal Committee's preferred scenario, as the cure proportion parameters take non-zero values from 5 years in both treatment groups. Of note, the company's new base case model still assumes that a certain proportion of people treated with adjuvant osimertinib are cured from 4 years (the warm-up period applies from year 4 to year 8) which is earlier than the time point for cure mentioned by the clinical advisors consulted by the company.

The EAG agrees that there is a precedent for the company's cure assumptions as a similar set of assumptions was applied in the model used to inform NICE TA876.[7] However, the Final Guidance Document (FDG) for this appraisal states that the EAG raised concerns around the lack of evidence to support the cure assumptions and the Appraisal Committee agreed that these assumptions were uncertain. In TA876, removing the cure assumption had only a small effect on the ICER for nivolumab. In the current appraisal of osimertinib, the cure assumptions are a key driver of the ICER for osimertinib (see Section 4, Table 3).

Overall, the EAG's view can be summarised as follows:

- The ADAURA trial[4] demonstrates that adjuvant osimertinib leads to statistically significant improvements in DFS and OS. The EAG's clinical advisors agreed that osimertinib is a valuable treatment in this setting, and that aside from adjuvant chemotherapy, which offers limited benefits, no other treatments are available for this patient population.
- The company's base case assumptions lead to modelled DFS hazards which deviate from the DFS hazard observed in ADAURA. The empirical (smoothed) hazard for the osimertinib group in ADAURA remains high at 5 years, which is not consistent with the assumption of cure (see Figure 1 and

- Figure ***2***).
- The modelled cure assumptions are the key driver of the cost-effectiveness of adjuvant osimertinib (see Section 4, Table 3).
- Similar cure assumptions (including a warm-up period) have been applied in previous NICE appraisals.[7, 8] However, in these previous appraisals, equivalent cure assumptions have been applied in both treatment groups and these have not been a key driver of the ICER. In both of these previous appraisals, these cure assumptions have been viewed with uncertainty by EAGs and Appraisal Committees.
- The company's new analyses of the absolute cured proportions in the model are mathematically incorrect and should be disregarded. The modelled benefits of osimertinib in avoiding/delaying relapse may be best understood through reference to the modelled DFS curves under alternative cure assumptions (see Figure 3).
- Whilst the company's DG response argues otherwise, the Appraisal Committee's preferred cure assumptions apply the same initial cure time point (starting at 5 years) in both treatment groups and are therefore consistent with clinical input obtained by the company.
- The EAG's optimistic and pessimistic scenarios suggest an ICER range of £17,156 to £51,952 per QALY gained (EAG report,[2] Table 55). When the Appraisal Committee's preferred assumptions for re-treatment and EGFR testing costs are also incorporated, the ICER range for the EAG's optimistic and pessimistic cure assumptions is higher at £25,820 to £61,665 per QALY gained. Given that no further data on recurrence are being collected in ADAURA, uncertainty around long-term DFS is unresolvable and there is not a strong basis for selecting any particular cure scenario for osimertinib within these ranges.

3.2 Retreatment assumptions (Company's DG response, Issue 2)

The company's model assumes that adjuvant osimertinib is given for a maximum treatment period of 3 years. The company's DG response[3] argues that the Appraisal Committee's preferred assumption of a 3 year time point for retreatment (i.e., immediately after the maximum adjuvant treatment period) is not clinically plausible. The company states that their original assumption of a 4-year retreatment time point was informed by interviews with clinical experts, the majority of whom agreed that they would leave at least a 12-month gap before retreatment.[6] The company's DG response highlights that the clinician interviews mentioned a minimum treatment break of 6 months. As such, the company's updated base case model includes retreatment from 42 months (3.5 years). The company states that this assumption is highly conservative.

The company's DG response also argues that the Appraisal Committee's preferred assumption around the retreatment rate is not supported by evidence and that the Committee's preferred estimate is lower than the estimate suggested by EAG's clinical advisors (70% versus 83%). The company's updated

base case model assumes a retreatment rate of 60%, based on the mid-point between the Appraisal Committee's preferred value and the company's original retreatment rate of 50%.

EAG critique

The company's DG response[3] does not provide any new evidence on the appropriate time point from which retreatment would be offered. The EAG believes that it may be reasonable to assume a retreatment time point of 3.5 years, but notes that in practice, clinicians may sometimes wish to retreat earlier if the patient discontinued osimertinib prior to completing 3 years of treatment. [redacted] The retreatment timepoint is not a key driver of the ICER (see Section 4, Table 3).

The company's DG response does not present any new evidence to inform the osimertinib retreatment rate. Whilst the company's DG response argues that the Appraisal Committee's preferred estimate is not supported by evidence and is lower than the estimate provided by the EAG's clinical advisors, the same is also true of the company's updated retreatment rate of 60%. Based on clinical advice, the EAG believes that it is plausible that a higher proportion of patients may be retreated in practice, although the true proportion remains unknown.

3.3 Age of the target population (Company's DG response, Issue 3)

The company's DG response[3] argues that the Appraisal Committee's preferred start age of 70 years from SACT[5] is inappropriate and is inconsistent with the age of diagnosis in ADAURA.[4] The company argues that the baseline characteristics applied in the model must ensure consistency with the most relevant source of evidence for the other model parameters (ADAURA). The company's response also states that clinicians interviewed by the company considered that the baseline characteristics in ADAURA were broadly representative of clinical practice.[6] The company's response refers to a survey of 233 UK patients conducted by EGFR Positive UK[9] in which the median age of respondents at diagnosis was 60-64 years. The company highlights that this is similar to the mean age of patients in ADAURA which is used in their base case model (63 years).[4]

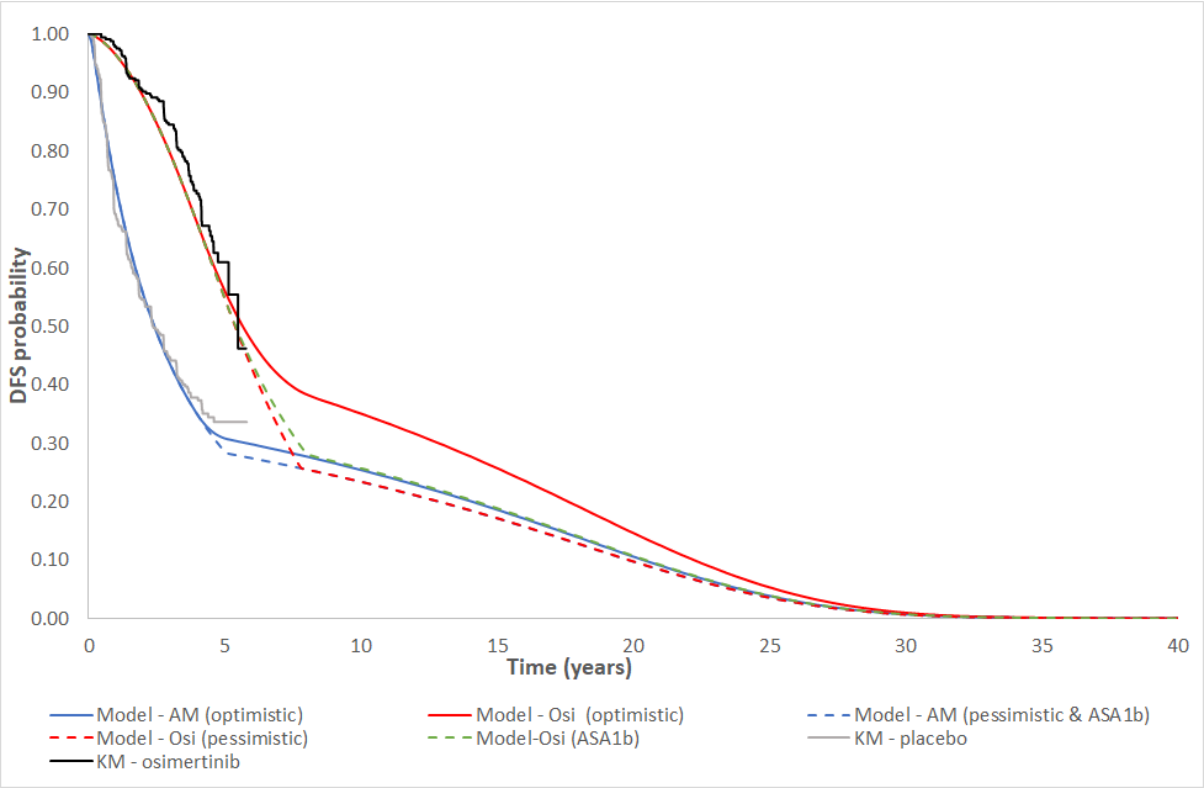
EAG critique

The company's DG response[3] refers to new evidence around patient age in the form of a survey conducted by EGFR+ UK.[9] A report describing this survey was shared with the EAG by the company. The survey report states that on average, most of the respondents were aged 60-64 years at diagnosis. However, 72% of the survey population had Stage 4 disease at diagnosis and therefore would not be

eligible to receive adjuvant osimertinib (although these patients were at a later stage of the disease when they were diagnosed). As such, the EAG does not believe that this survey reflects the target population for this appraisal.

The EAG agrees with the company that applying a model start age of 70 years based on SACT[5] does introduce some inconsistency between the evidence sources used to inform patient characteristics and time-to-event outcomes in the model. The EAG notes that when the initial age of 70 years is applied in the model, the model-predicted DFS function provides a worse fit to the observed DFS outcomes for the osimertinib group of ADAURA due to increased risks of all-cause mortality for older patients (see Figure 4). However, SACT reflects data on the use of osimertinib in the NHS and therefore should, at least in principle, reflect the actual age of the target population for adjuvant osimertinib. As noted in Section 4.2.5 of the EAG report,[2] the EAG's clinical advisors commented that the median age of patients in ADAURA was relatively young for an NSCLC population but that it may be generalisable to an EGFR mutative-positive NSCLC population. The EAG also notes that the number of patients included in the SACT dataset is fairly small (N=143). The inclusion of an older age leads to a fairly large increase in the ICER (see Section 4, Table 3).

Figure 4: Model-predicted DFS – EAG optimistic scenario, EAG pessimistic scenario and Appraisal Committee-preferred scenario (starting age = 70 years)



Whilst not mentioned in the company's DG response, the EAG notes that the previous appraisal of neoadjuvant nivolumab plus chemotherapy for NSCLC applied a model start age of 64 years,[7] which is similar to the mean age in ADAURA.[4] Whilst this previous appraisal does not relate to an EGFR mutation-positive population, the use of the age in the trial in TA876 and the age in the SACT data in this appraisal may lead to some inconsistency.

The EAG also notes that outcomes data for patients who experience distant recurrence in the model are drawn from the FLAURA trial.[10] This study enrolled patients with a median age of 64 years, which is younger than the median age in SACT. Assuming an older start age in the model leads to additional inconsistencies between modelled patients with and without distant relapse.

3.4 EGFR testing costs (Company's DG response, Issue 5)

The company's DG response[3] argues that EGFR mutation testing is routinely conducted in the UK and that testing costs are not attributable to osimertinib and should be excluded from the model.

EAG critique

The EAG agrees that most patients will undergo EGFR testing via next-generation sequencing (NGS). However, as noted in Section 5.3.6 the EAG report,[2] the EAG believes that some of the costs of EGFR

testing are attributable to adjuvant osimertinib and that these should be considered, at least in sensitivity analyses. The inclusion of EGFR testing costs is not a key driver of the ICER as it impacts on both treatment groups in the model (see Section 4, Table 3).

3.5 Misrepresentations and factual inaccuracies discussed in the company's DG response

The EAG notes the following points regarding apparent misrepresentations and factual inaccuracies listed in the company's DG response:[3]

1. Owing to uncertainty around long-term DFS and OS outcomes, the EAG does not have a single preferred base case. Rather, the EAG's exploratory analyses were presented based on optimistic and pessimistic preferred scenarios.
2. NICE Guidance for TA761 does not state a preference for the EAG's pessimistic scenario. Both the EAG's optimistic and pessimistic analyses are mentioned in the guidance document.
3. The EAG's clinical advisors did not explicitly state that a warm-up period should be included. As noted in Section 3.1, one of the EAG's clinical advisors commented that the company's base case model predictions were potentially plausible but uncertain.
4. The EAG believes that osimertinib should be appraised based on the evidence available for this technology. The EAG agrees with the company that making generalised assumptions about the efficacy and mechanism of action of adjuvant osimertinib based on older-generation tyrosine kinase inhibitors should be avoided.

4. Additional analyses undertaken by the EAG

Table 3 summarises the individual impact of reintroducing the Appraisal Committee's preferred assumptions into the company's new base case model. As shown in the table, the assumptions related to cure time point for adjuvant osimertinib have the greatest impact on the ICER.

Table 3: Additional analysis undertaken by the EAG – impact of re-introducing the Appraisal Committee's preferred assumptions into the company's new base case model

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's new post-DG base case (deterministic)							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,897**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred assumption 1: Using the EAG's corrections for model and costing errors (including EGFR testing costs)							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,727
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred assumption 2: No warm-up period prior to cure, cure point of 5 years for AM, 8 years for osimertinib							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,085
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred assumption 3 & 4: Cure-point of 5 years for active monitoring, cure-point of 5 years plus time on treatment (1-TTD function) for osimertinib							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,344
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred assumption 5: Retreatment allowed from 3 years after starting osimertinib							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,204
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred assumption 6: 70% of osimertinib retreatment in the first-line metastatic setting							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,517
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred assumption 7: Starting age = 70 years							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,257
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred analysis (deterministic), with starting age = 63 years							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,556**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-
Appraisal Committee's preferred analysis (deterministic), with starting age = 70 years							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£57,450**
AM	[redacted]	[redacted]	[redacted]	-	-	-	-

QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; DG - draft guidance; AM - active monitoring; TTD - time to treatment discontinuation

** Undiscounted*

5. References

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